DISSERTATION

THE TOTAL SYNTHESIS OF (+)-PARAHERQUAMIDE B

Submitted by

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In partial fulfillment of the requirements

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WE HERBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY **TIMOTHY D. CUSHING** ENTITLED *THE TOTAL SYNTHESIS OF (+)-PARAHERQUAMIDE B* BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Comittee on Graduate Work

Adviser

Department Head

ABSTRACT

THE TOTAL SYNTHESIS OF (+)-PARAHERQUAMIDE B

The first stereocontrolled total synthesis of (+)-paraherquamide B is described in 42 chemical steps. The synthesis is a convergent one, starting from S-proline and vanillin. Vanillin was acylated, nitrated and hydrolyzed to supply o-nitrovanillin (**131**). This was converted to the azlactone, hydrolyzed to the α-ketocarboxylic acid, oxidatively decarboxylated and reductively cyclized to afford the oxindole **142**. The oxindole was demethylated, regioselectively prenylated, epoxidized, and subjected to a key seven-membered ring forming procedure to provide the unique dioxepin **124**. This ring forming methodology was explored in detail with two alternative procedures (epoxidation/$SnCl_4$; PhSeCl, N-PSP) culminating in the synthesis of the dioxepins **148**, **154**, **188**, **189**, **192**, **195**, **193**, and **196**. **124** was reduced, protected and subjected to a Mannich reaction to afford the gramine **220** in 4% overall yield. S-proline was condensed with pivaldehyde and allylated to give the key (Seebach) heterocycle, which was amidolyzed, cyclized, ozonolyzed and homologated to grant the (Williams) piperazinedione **91**. This was oxidatively N-deprotected, reduced, O-silylated and dimethoxycarbonylated to afford the piperazinedione **271** in 20% yield from proline. This piperazinedione was alkylated with **220** to yield the indole **272**, which was demethoxycarbonylated to provide two separable diastereomers **273** and **274**. These were individually treated with Me_3OBF_4, $(BOC)_2O$, and n-Bu_4NF to afford the diols **276** and **293**. The allylic alcohols were converted to the chlorides, and resilylated to supply **290** and **295**, which were subjected to a key regioselective S_N2' cyclization. The resulting bicyclic piperazinedione **291** was cyclized, selectively reduced, N-methylated and deprotected to provide the indole-

piperazinone **311**. This indole-piperazinone **311** was oxidatively spiro–cyclized and dehydrated to afford (+)-paraherquamide B (**3**) in 1.4% yield from S-proline.

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ACKNOWLEDGEMENTS

In the course of this synthesis, there have been numerous colleagues and coworkers who played a role in the success of this work. I would like to thank especially the following people: Byung Lee, taught me a great deal about how to do reactions and patiently answered many of my questions; Paul Erhlich was very encouraging and gave plenty of useful advise in my early days as a graduate student; Tomas Glinka not only was an excellent role model, he also laid the foundation for all this work, his input into this project was invaluable.

In particular, I would like to thank Professor Juan F. Sanz-Cervera. Without his assistance; technically, intellectually and inspirationally this work would not have born such delicious fruit. His ability to elucidate structure from very complex spectra was extraordinary. This partnership forged in the last stages of the synthesis was the high point of my career as a graduate student.

Over the years others who helped me both professionally and personally include ; Dave Aldous, Jinau Cao, Mark Flannigan, Tom Gant, Peter Lander, Bill Leonard, Russ Lewis, Judi Pogge, Mark Sabol, Pete Sinclair, and Chenguang Yuan. Thanks are in order to the four people who had to put up with my ranting and raving the longest of all; Sean Esslinger, Glenn Fegley, Jim Hendrix, and Greg Miknis. Dan Bond was instrumental for much of the success of this synthesis. He came on knowing very little organic chemistry and soon he was quickly making large quantities of the oxindole precursors, eventually operating completely independently.

Finally, I would like to thank Professor Robert M. Williams who faithfully provided the financial resources that allowed me to work with almost no constraints. Additionally, he discovered very early on how to motivate me, and had an amazing knack for knowing exactly when I needed that encouragement. Most importantly, his intellectual and creative input was paramount. The late Prof. R. B. Woodward said "plan in detail,

then carry it out " The first half of this credo is demonstrated quite effectively by a comparison of Prof. Williams synthetic plan outlined in chapter one (Scheme 32) and the actual final synthesis (Schemes 109 and 111), they are remarkably similar.

DEDICATION

For my parents

and my

son, Peter

TABLE OF CONTENTS

ABBREVIATIONS

Ac_2O	acetic anhydride
AcOH	acetic acid
Bn	benzyl
BOC	*tert*-butoxycarbonyl
$(BOC)_2O$	di-tert-butyl dicarbonate
BSTFA	bis(trimethylsilyl)trifluoroacetamide
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CNS	central nervous system
m-CPBA	*meta*-chloroperbenzoic acid
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCU	1.3-dicyclohexylurea
DIBAL	diisobutylaluminum hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DMEA	dimethylethyl amine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol

HMPA	hexamethylphosphoramide
im	1-imidazolyl
LDA	lithium diisopropylamine
MeOH	methanol
MOM	methoxymethyl
Ms	methanesulfonyl (mesylate)
MTPI	methyl triphenoxyphosphonium iodide
NCS	N-chlorosuccinimide
N-PSP	N-(phenylseleno)phthalimide
pMB	p-methoxybenzyl
PPTS	pyridinium p- toluenesulfonate
PTLC	preparatory thin layer chromatagraphy
pv	pivaloyl
Py	pyridine
TBDMS	tert-butyldimethylsilyl
t-BDMSCl	*tert*-butyldimethylsilyl chloride
t-BDMSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TBDPS	t*ert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-BuOH	*tert*-butanol
Tf	trifluoromethanesulfonate
TFAA	trifluoroacetic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl

TMSI	trimethylsilyl iodide
TS	toluenesulfonyl

CHAPTER ONE

INTRODUCTION

1.1 Introduction

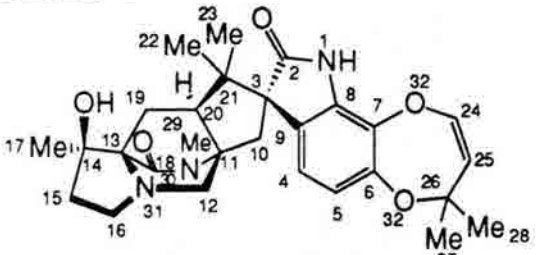
Most scientific research is a continually evolving process. In a synthesis of any length there are problems encountered that must be either overcome or sidestepped. This is exactly the case herein. Our initial efforts were directed toward the total synthesis of (–)-paraherquamide A (**1**), but because of complications, we were forced to fall back on the slightly simpler (+)-paraherquamide B (**3**) (Scheme 1). Thus, another title would be; An approach toward the synthesis of paraherquamide A; the total synthesis of (+)-paraherquamide B. (+)-Paraherquamide B (**3**) is the enantiomer of the natural product (–)-paraherquamide B (**2**). In principle, **2** could have been made, if we had started with the unnatural amino acid D-proline instead of the natural L-proline. This was simply a matter of expense.

Today, many question the usefulness of total synthesis: the construction of complex molecules is unnecessary; synthetic organic chemistry should be restricted to developing new methods (methodology). There are many ways to respond to this argument. Total synthesis by its very nature explores most intimately the properties of molecules. This is particularly relevant when the molecule is some important pharmacological agent. Perhaps some intrinsic property can be found that could aid in more potent analogs. The total synthesis of natural products can also tell us much about the biosynthesis of the molecule, which may have many useful applications in other fields, such as biology. One must question the alternative activity of synthetic organic chemists. What is the point of developing new methods of synthesis when they are never used or applied? What has been demonstrated or obtained? The worthiness of a reaction is always proved when it is used successfully in a synthetic sequence on a molecule of some complexity. Finally, the act of total synthesis can also uncover new reactions and methods that could be useful in later endeavors. In this work, I believe that many of these points have been made.

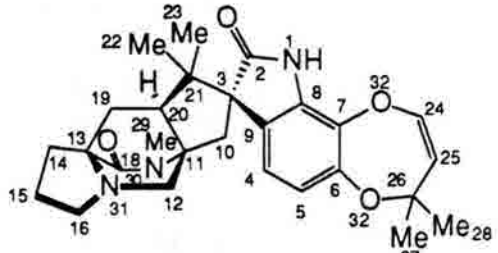
1.2 Background and Significance

Paraherquamide A (**1**) a toxic metabolite, was first isolated from the mold *Penicillium paraherquei* in 1980 by Yamazika.[1] Relevant data (NMR, IR, UV, MS) was obtained, including a single crystal X-ray structural analysis that firmly established the structure and relative stereochemistry of this molecule. In 1989 [2] an investigation by a synthetic group at Merck Sharp & Dohme conclusively established the absolute configuration (Scheme 1).

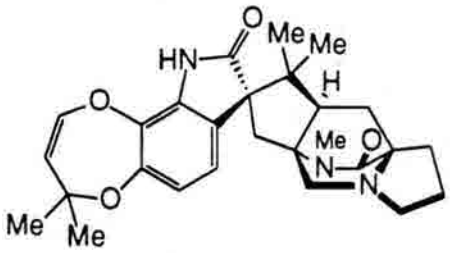
Scheme 1



(–)-paraherquamide A, **1**



(–)-paraherquamide B, **2**

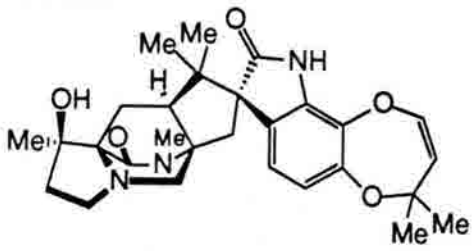


(+)-paraherquamide B, **3**

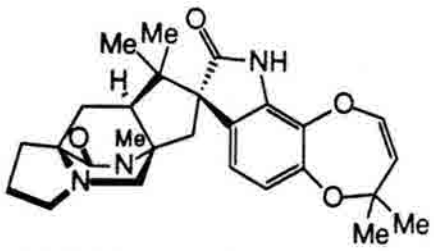
In 1990 another group at Merck isolated Paraherquamide A (**1**) and six structurally related compounds (Paraherquamides B–G) from the fermentation broth of *Penicillium charlesii* (ATCC 20841).[3] A similar group from SmithKline Beecham discovered paraherquamide A (**1**) and three of the six previously mentioned paraherquamides from an organism found in the soil at Kemer, Turkey.[4] This strain was later identified as a penicillium species. The growing interest in paraherquamide A (**1**) (and the other paraherquamides) has come from the finding that it has a high anthelmintic activity.[5] After this revelation, paraherquamide A (**1**) was intensively studied, in an attempt to elucidate

both the chemical and pharmacological properties of this molecule. To date, a number of patents relating to the culture and isolation have been proffered (Scheme 2).

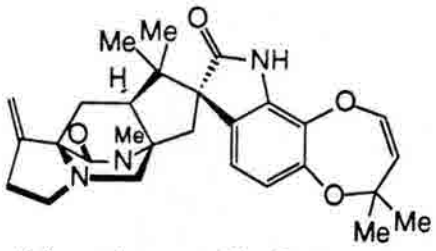
Scheme 2



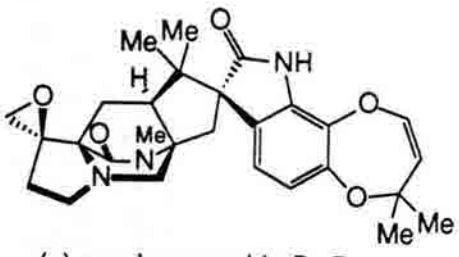
(–)-paraherquamide A, **1**



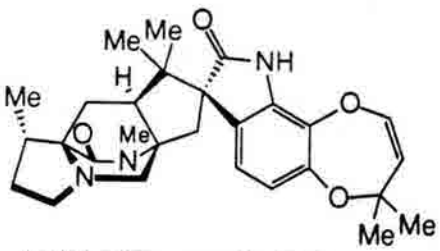
(–)-paraherquamide B, **2**



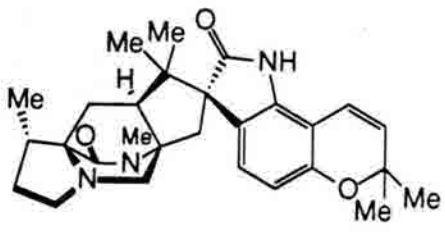
(–)-paraherquamide C, **4**



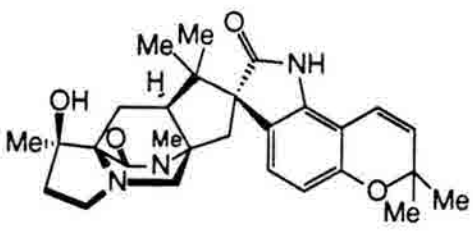
(–)-paraherquamide D, **5**



(–)-Paraherquamide E, **6**



(–)-paraherquamide F, **7**



(–)-paraherquamide G, **8**

The importance of a new antinematodal (anthelmintic) agent cannot be overstated. Helminths or intestinal nematodes, infect large numbers of livestock world wide, leading to sickness or death of the host animal. The devastation this has on the farmer or stock owner is immeasurable. It not only causes financial losses, but also increased human suffering. This is particularly painful to those people who depend entirely on their animals for sustenance. Today there are essentially three classes of broad spectrum anthelmintics: the benziimidizoles, the levamisoles/morantel and avermectins/milbemycins. Unfortunately the first two groups have lost much of their original anthelmintic activity because of resistance built up by the helminths.[6] Lately the third group has also started to show inactivity against various parasites.[7] Paraherquamide A and the other paraherquamides represents a brand new class of antiparisitic agents. They could play a large role supplanting, or complementing the other anthelmintics currently on the market.

1.3 Physical–Chemical and Structural Characteristics

Yamazaki[1b] reported the following characteristics of Paraherquamide A, **1**; colorless prisms, 244–247 °C (decomposition), $[\alpha]_D^{22}$ –28° (c = 0.43, CH_3OH), $C_{28}H_{35}N_3O_5$ (M+ m/e 493), UV λ max (EtOH) nm (ε): 226 (32400), 260 (6100), 290 (1600); IR ν (KBr) 3510, 3430, 3245,1714, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (3H, s); 1.10 (3H, s); 1.45 (6H, s); 1.85 (1H, d, J = 15Hz); 1.77–2.40 (5H, m); 2.55 (1H, d, J = 11Hz); 2.58 (1H, s, D_2O exch.); 2.67 (1H, d, J = 15Hz); 2.93–3.25 (2H, m); 3.03 (3H, s); 3.58 (1H, d, J = 11Hz); 4.87 (1H, d, J = 8Hz); 6.30 (1H, d, J = 8Hz); 6.64 (1H, d, J = 8Hz); 6.78 (1H, d, J = 8Hz); 8.33 (1H, s, D_2O exch.). A Dragendorf test gave a positive color. Crystals were grown in ethyl acetate and an X-ray diffraction pattern obtained, establishing the relative stereochemistry. Later, workers at Merck & company [3] published data from ^1H NMR spectra taken in CD_2Cl_2 and $(CD_3)_2CO$. They also reported data from a ^{13}C NMR spectrum in CD_2Cl_2. They made the carbon and proton assignments from these and also a one-bond ^{13}C–^1H chemical shift correlation experiment (HETCOR); ^1H NMR (400MHz) (CD_2Cl_2) δ 0.84 (3H, s, 23-H); 1.08 (3H, s, 22-H); 1.41 (3H, s, 27-

H); 1.43 (3H, s, 28-H); 1.56 (3H, s, 17-H); 1.75 (1H, dd, J = 10.5, 12.5Hz, 19-Hβ); 1.77 (1H, dd, J = 10.8, 10.8Hz, 19-Hα); 1.80 (1H, m, 15-Hα); 1.87 (1H, d, 15.6Hz, 10-Hβ); 2.18 (1H, m, 16-Hα); 2.24 (1H, m, 15-Hβ); 2.55 (1H, d, J = 2.2, 11.0Hz, 12-Hα); 2.65 (1H, d, J = 16.1Hz, 10-Hα); 2.66 (1H, br s, D_2O exch, 14-OH); 2.96 (1H, ddd, J = 2.0, 10.3, 10.3Hz, 20-H); 2.99 (3H, s, 29-H); 3.17 (1H, m, 16-Hβ); 3.58 (1H, d, J = 10.8Hz, 12-Hβ); 4.90 (1H, d, 6.8Hz, 25-H); 6.32 (1H, d, J = 7.8Hz, 24-H); 6.68 (1H, d, J = 7.3Hz, 5-H); 6.84 (1H, d, J = 7.3Hz, 4-H); 7.50 (1H, br s, D_2O exch, 1-H), (proton assignments as numbered according to CA) (Scheme 1). They reported a UV λ max (methanol) of 225nm (logε = 4.50) and a Rf value of 0.51 using Whatman KC18F reverse phase TLC: methanol/H_2O (8:2). Mass spectral data was also reported; $C_{28}H_{35}N_3O_5$ 493 m/e M^+ (493) (434) (165) 163). They found paraherquamide A (**1**) soluble in methanol, ethyl acetate, acetone, and dimethylsulfate but essentially insoluble in water. Paraherquamide A responded to iodine and 50% H_2SO_4. Workers at SmithKline Beecham performed similar work including a 2D ^1H, ^{13}C COSY NMR experiment and obtained the same structural assignments as the Merck group. The absolute configuration for paraherquamide A (**1**) was established via an X-ray crystal analysis of a heavy atom containing semi-synthetic analog (to be described subsequently). Similar data was obtained for paraherquamide B (**2**);[3] ^1H NMR (400MHz) (CD_2Cl_2) δ 0.83 (3H, s, 23-H); 1.09 (3H, s, 22-H); 1.39 (1H, m, 15-Ha); 1.41 (3H, s, 27-H); 1.43 (3H, s, 28-H); 1.64 (1H, dd, J = 10.4, 12.4Hz, 19-Hb); 1.83 (2H, m, 19-Ha, 14-H); 1.87 (1H, d, 15.1Hz, 10-Hb); 2.13 (2H, m, 15-Hb, 16-Ha); 2.49 (1H, m, 14-H); 2.61 (1H, dd, J = 1.0, 11.5Hz, 12-Ha); 2.67 (1H, d, J = 15.2Hz, 10-Ha); 2.98 (1H, m); 3.01 (3H, s, 29-H); 3.03 (1H, m, 16-Hb); 3.59 (1H, d, J = 10.9Hz, 12-Hb); 4.89 (1H, d, 7.7Hz, 25-H); 6.32 (1H, d, J = 7.7Hz, 24-H); 6.67 (1H, d, J = 8.2Hz, 5-H); 6.85 (1H, d, J = 8.2Hz, 4-H); 7.41 (1H, br s, D_2O exch, 1-H), (the numbering is the same as paraherquamide A but without #17). A 2D ^1H, ^{13}C COSY NMR experiment together with mass spectral data; MS (EI) $C_{27}H_{33}N_3O_4$ 463.2488 *m/e* (rel intensity) 463 (M^+, 4) 404 (78) 135 (48) 133 (100), led

the Merck workers to propose the structure as drawn in Scheme 1, with the proton assignments made from the NMR spectra (above). They also reported the following data; UV λ max (methanol) of 225nm, Rf value of 0.42 using Whatman KC18F reverse phase TLC: methanol/H_2O (8:2). This compound has similar solubility characteristics to paraherquamide A (**1**); it was soluble in methanol, ethyl acetate, acetone, and dimethyl-sulfate but was essentially insoluble in water. Paraherquamide B (**2**) also responded to iodine and 50% H_2SO_4. The Merck workers performed detailed spectroscopic work (COSY,HETCOR, NOE, MS) on the other paraherquamides (C–G) and obtained the structures shown in Scheme 2. They reported similar spectral characteristics for all seven compounds. As would be expected, the only major change in the nmr spectra stemmed from the signals contained on the proline ring (except paraherquamides E–F). The chemical shifts of the other signals were quite close. This can be gleaned from a perusal of the proton nmr spectral data of paraherquamide A & B. The conclusions reached by the Merck group, were independently confirmed by the SmithKline workers for paraherquamides A & E–G. They concluded that the relative stereochemistry must be the same for all seven analogs. The Merck group also reported that the absolute stereochemistry for the other six products was the same as paraherquamide A (**1**).

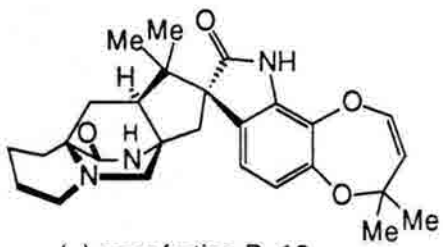
1.4 Relatives of the Paraherquamides

The paraherquamides are structurally very similar to the marcfortines (A-C), and the brevianamides (A-B). Marcfortines A, B, C were isolated from *Penicillium roqueforti* (strain B26) in 1980 by Polonsky.[8] The similarities between the paraherquamides and the marcfortines is striking, the only difference between paraherquamide B (**2**) and marcfortine A is that marcfortine A contains a pipecolic residue instead of a proline unit. The marcfortine structures were solved by X-ray diffraction. Patterns were obtained for both A and C. This data confirmed that the paraherquamides and marcfortines have the same relative stereochemistry. As would be expected, the published nmr data for marcfortine A is similar to that of the paraherquamides (A–E). Similarly, marcfortine C has the identical

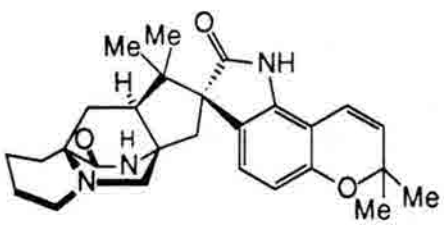
pyran ring system as in paraherquamides F and G (and similar nmr characteristics), but marcfortine B and C lack the N-methyl group found in marcfortine A and all the paraherquamides. The paraherquamides also have structural features reminiscent of the brevianamides, a class of compounds that have been somewhat better studied [9]. (+)-Brevianamide B (**12**) is similar to the paraherquamides in that it contains the same proline moiety as well as the bicylco [2.2.2] ring structure. Interestingly, the bicyco [2.2.2] ring system of (+)-brevianamide A (**13**) possesses the opposite absolute configuration relative to (+)-brevianamide B (**12**), the paraherquamides and marcfortines (Scheme 3).

Scheme 3

(–)-marcfortine A, **9**

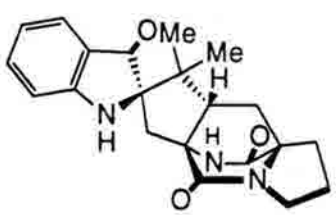


(–)-marcfortine B, **10**



(–)-marcfortine C, **11**

(+)-brevianamide B, **12**

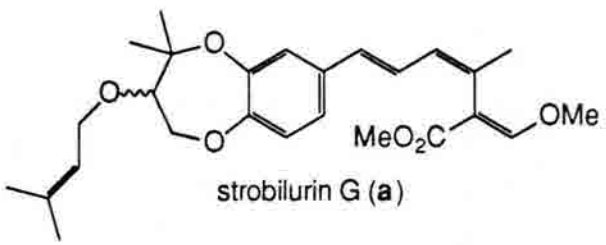


(+)-brevianamide A, **13**

The close structural similarities of all these compounds clearly imply a very similar biogenesis. It is useful to describe the structural features from this standpoint. The paraherquamides and brevianamides (A & B) appear to be derived from the condensation of

tryptophan and a proline. In the case of paraherquamide A it is a unique 2-hydroxy-2-methyl proline. The marcfortines, on the other hand, appear to come from the condensation of tryptophan and pipecolic acid. In the case of the marcfortines and paraherquamides the resulting dioxopiperazine is converted to a monooxopiperizine, a process that is known[10] The paraherquamides, marcfortines and brevianamides all incorporate an isoprene unit that forms a bridge over the oxopiperizine structure. The paraherquamides and marcfortines differ from the brevianamides in that a second isoprene unit coupled with an oxidized form of tryptophan give the dioxepin (or pyran) moiety. This is one of the most interesting and unique features of these compounds. The *gem*-dimethyl dioxepin ring found in paraherquamides A–E and the marcfortines A & B has never been found in any other natural product. A similar structural feature was discovered in an antifungal antibiotic natural product strobilurin G (**a**) isolated from *Bolinea lutea* [11] by some workers at Ciba–Geigy. Its dioxepin is similar, but lacks the double bond found in the other metabolites (Scheme 4).

Scheme 4

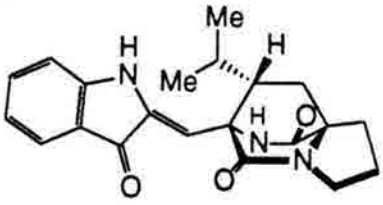


strobilurin G (**a**)

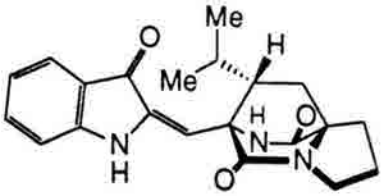
The variation among the paraherquamides themselves is also quite interesting. It appears that the differences in the C-14 position of the proline ring in paraherquamides (B–G) are simply changes in the more complex parent paraherquamide A (**1**). At what stage in the biosynthesis these transformations take place is unknown.

The paraherquamides, marcfortines and brevianamides belong to a large group of natural products containing a diketopiperazine moiety, produced from the condensation of two amino acid subunits. This group includes such notable toxins as the echinulins, gliotoxins and the sporidesmins.

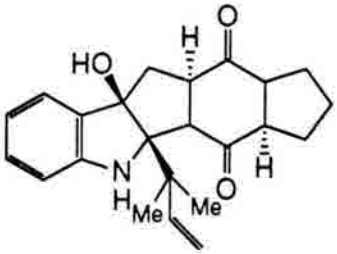
Scheme 5



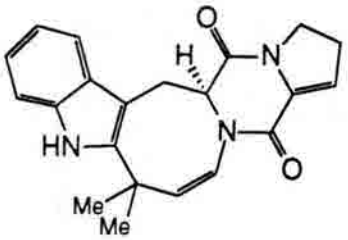
brevianamide C, **14**



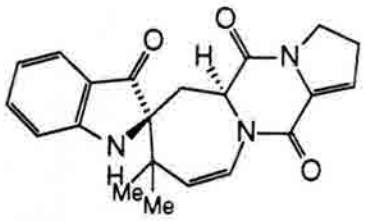
brevianamide D, **15**



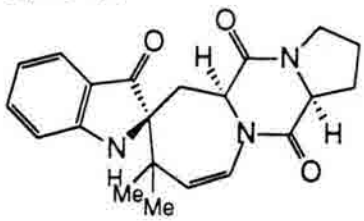
brevianamide E, **16**



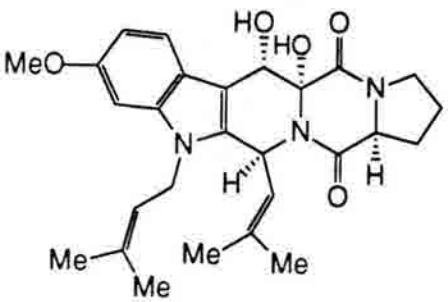
10,20-dehydro[12,13-dehydro-proly]-2-(1',1'-dimethyl-allyltryptophyl) diketo-piperazine, **17**



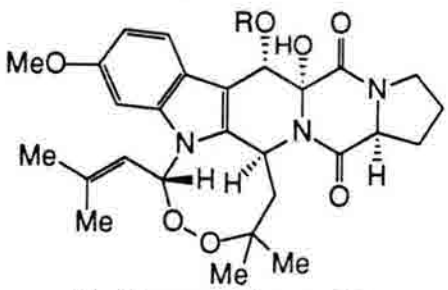
austamide, **18**



12,13-dihydroaustamide, **19**



fumitremorgen B, **20**

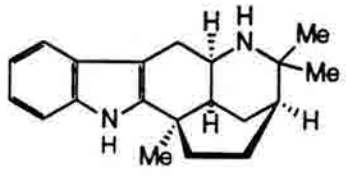


R = H; verruculogen, **21**
R = $Me_2C{=}CHCH_2$, fumitremorgen A, **22**

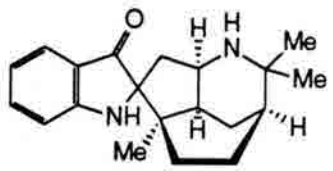
The paraherquamides and brevianamides are also members of a smaller subset of this group, characterized by the condensation of a proline and a tryptophan (Scheme 5). This group of mold metabolites includes; the austamides (*Aspergillus ustus*), fumitremorgens (*Aspergillus fumigatus, Penicillium lanosum, A. caespitosus, P. piscarium*) and veruculogen (*P.verruculosum, P. paxilli, P. estinogenum, A. caespitosus, A. fumigatus, P. piscarium*). The latter was also found in *Penicillium paraherquei..*[12]

It was proposed that the disubstituted indolic compound **17** is a biosynthetic precursor of austamide (**18**) itself [13] (Scheme 5). This particular type of biosynthetic oxidation is known to take place among many different groups of monoterpenoid indoles.[14] One example is in the aristotelia group. It is thought that aristotelone (**24**) is directly evolved from aristoteline (**23**). Similar oxidations are assumed to take place within the mitragyna class (corynatheine–heteroyohimbine group). For example the oxindole alkaloids rhynchophylline (**26**) and isorhynchophylline (**27**) are thought to be derived from the corresponding secoyohimbine, dihydrocorynantheine (**25**). This is also illustrated by the close structural relationship between tetrahydroalstonine (**28**) and the oxindole isopteropodine (**29**) [14,15]. Contained within the sarpagine–ajmaline–akuammiline group are some of the most complex indole alkaloids known.[14] It has been hypothesized that the oxindole alkaloid gelselegine (**34**) isolated from *Gelsemium elegans* is biosynthetically derived from a tetrahydrocarbozole koumidine (**31**). [16] The potent CNS stimulant and acetylcholine antagonist, gelsemine (**33**) (*Gelsemium sempervirens*) is also thought to be derived from this pathway. [17] Interestingly, it has been found that strictosidine (**30**) is in fact a precursor for many different alkaloids including those of the *Corynanthe–Strychnos* type [14] (Scheme 6). This type of oxidative spiro-cyclization described above, has a direct bearing on the possible biosynthesis of the brevianamides, marcfortines and paraherquamides. Since, these molecules are also indoxyls and oxindoles and would prove essential to effect the total synthesize of brevianamide B and (+)-paraherquamide B (**3**).

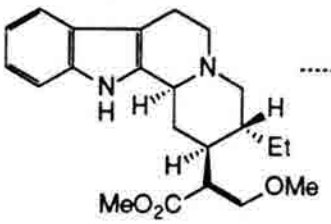
Scheme 6



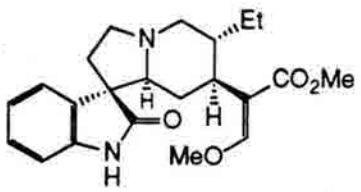
aristoteline, **23**



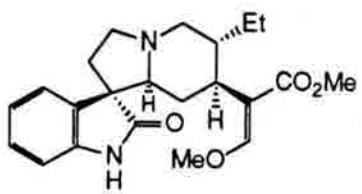
aristotelone, **24**



dihydrocorynantheine, **25**



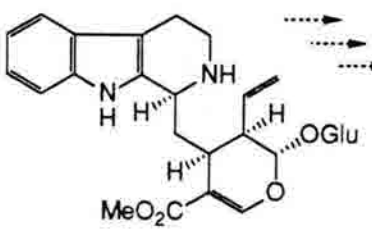
rhynchophylline, **26**



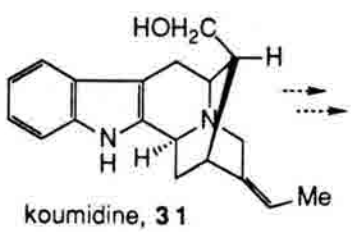
isorhynchophylline, **27**

tetrahydroalstonine, **28**

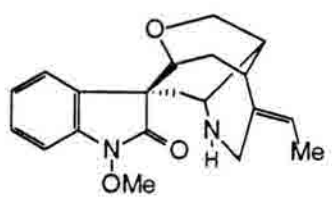
isopterpodine, **29**



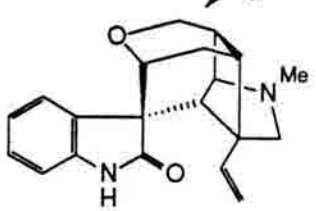
strictosidine, **30**



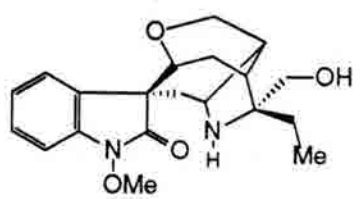
koumidine, **31**



rankinidine, **32**



gelsemine, **33**

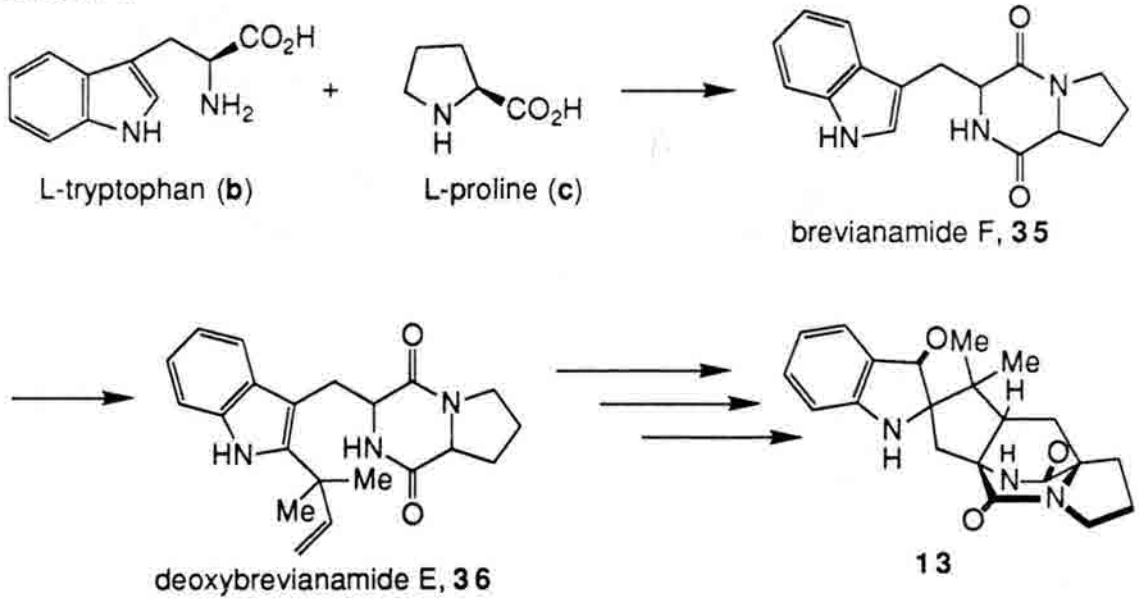


gelselegine, **34**

1.5 Biosynthesis

To date there has been no work done to elucidate the biosynthesis of the paraherquamides or marcfortines, but a fair amount of work has been done on the biosynthesis of the brevianamides. There is close structural similarities between all these molecules, so it is instructive to discuss them. The brevianamides A and B (Scheme 3 & 4) were first isolated by Birch and Wright in 1969 [9] from the culture extracts of *Penicillium brevicompactum*.. Brevianamide A (**13**) was also found in *Penicillium viridicatum* [18] and *Penicillium ochraceum*. [19] Four other brevianamides (C–F) were also found, but brevianamides C & D were later thought to be artifacts. Feeding experiments involving ^{14}C and ^{3}H labeled tryptophan, L-proline and mevalonic acid showed incorporation of these labels into both brevianamide F (**35**) and brevianamide A (**13**). Also, labeled brevianamide F (**35**) was shown to lead directly to brevianamide A (**13**). This induced Birch [12d] to propose a biosynthesis for this natural product (Scheme 7).

Scheme 7

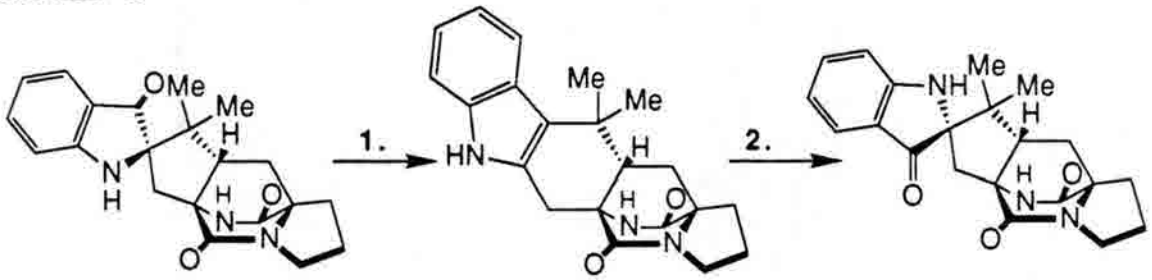


A short time later an x-ray crystal diffraction pattern was obtained on 5-Br-brevianamide A.[20] This established the correct structure as put forth by Birch but also unequivocally established the relative and absolute stereochemistry of brevianamide A (**13**). Earlier, Sammes had made the provocative suggestion that an oxidized form of **36**

(a pyrazine) could undergo an intramolecular [4+2] cyclization providing **13**.[21] Birch seemed to discount this because of the "inactive nature of the double bond"[22]; however, this hypothesis became even more enticing when brevianamide B (**12**) was found to incorporate a proline unit with the unnatural (R) configuration. This could be explained nicely by the intermediacy of an achiral azadiene **39**, which would cyclize in a [4+2] fashion to give the natural product. A synthetic strategy toward the total synthesis of brevianamide A and B was developed incorporating this idea.[23]

Birch and coworkers also did some degradation work to help in determining the structure of various brevianamides. Brevianamide A (**13**) was reduced, and subjected to acid catalyzed rearrangement (2N HCl) to give deoxybrevianamide A (**37**), which was then reoxidized (O_2/PtO_2/EtOAc or air/MeOH) to give brevianamide B [9b] (Scheme 8).

Scheme 8



(+)-brevianamide A, **13** deoxybrevianamide A, **37** (–)-brevianamide B, **38**

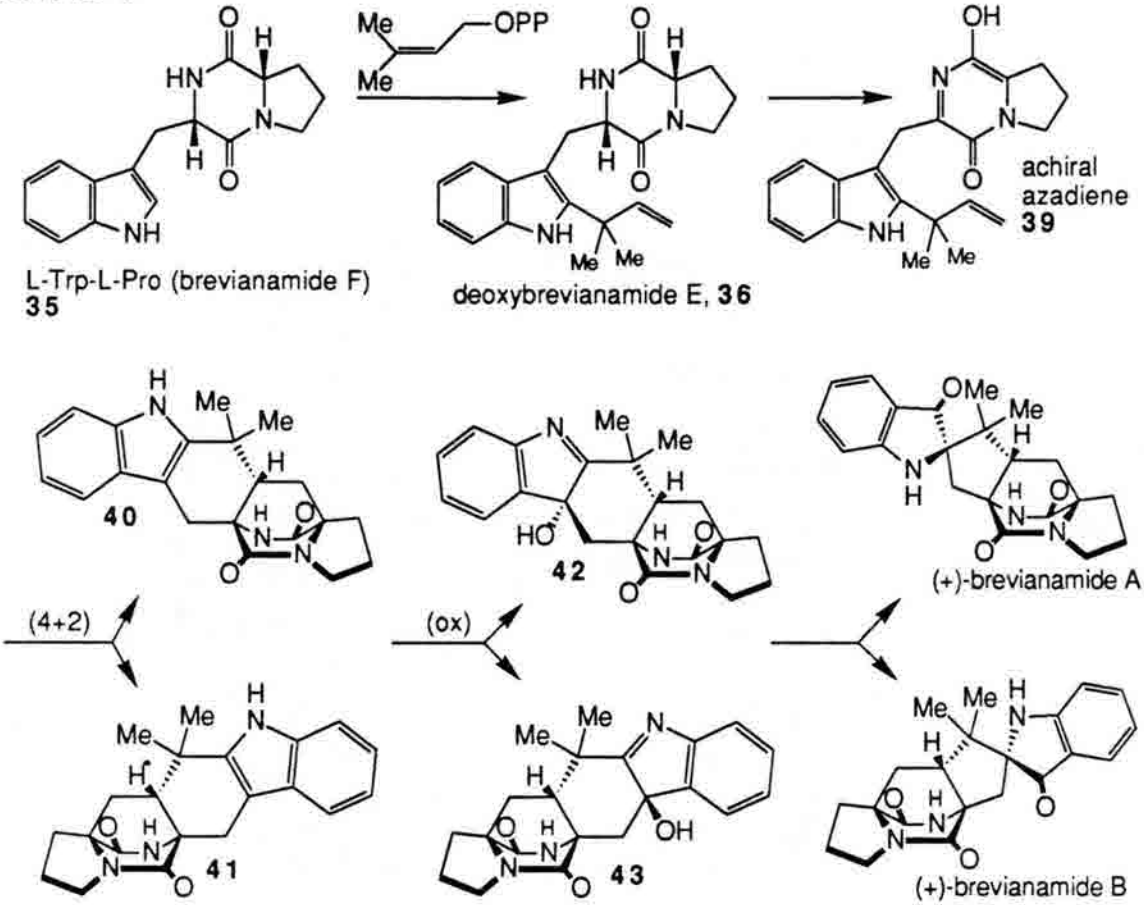
1a. $NaBH_4$, EtOH, then NaOH; **1b.** 2N HCl; **2.** O_2, PtO_2, EtOAc, or air, MeOH

Williams,*et al.* by total synthesis [24] refuted the proposed structure of this semi-synthetic brevianamide B (**38**). They showed that Birch had made the enantiomorph of the natural brevianamide B (**13**). This finding proved highly interesting because it appeared that *Penicillium brevicompactin* produced the bicyclo[2.2.2] ring system of brevianamide A and B as two distinct enantiomorphs. In light of these facts, Williams theorized that deoxybrevianamide E (**36**) was oxidized and enolized to give the achiral azadiene **39**, which would then undergo a [4+2] cycloaddition to give the enantiomeric hexacyclic indoles **40** and **41**. Oxidation, followed by a pinacol type rearrangement would produce brevianamide A (**13**) and brevianamide B (**12**) (Scheme 5). Williams and coworkers set

out to test this hypothesis. First, they decided to see if the proposed intermediate hexacyclic indoles **40** and **41** would incorporate into brevianamide A and B if fed to *Penicillium brevicompactin*. The synthesis of these enantiomorphic indoles followed the original (–)-brevianamide B synthesis. The necessary ^{13}C label was placed in the molecule with ^{13}C formaldehyde during a Mannich reaction. *Penicillium brevicompactin* was grown on a medium enriched with the newly synthesized ^{13}C-hexacyclic indoles **40** and **41** but, they found no incorporation of the ^{13}C-label in any of the brevianamide A or B. This failure to find any ^{13}C labelled products led them to question the intermediacy of these hexacyclic indoles. They tried to isolate the hexacylic indoles **40** and **41** from cultures of plain *Penicillium brevicompactin*, but even employing various analytical isolation techniques, they found no trace of the desired material. The failure to find any evidence for the hexacylic indoles **40** and **41** is somewhat surprising considering how this type of intermediate is commonly found in the biosynthesis of oxindole and indoxyl alkoloids, but there was additional evidence discounting these intermediates. It was found that an oxidation of the hexacyclic indole **40** by m-CPBA takes place on the least hindered face (β–) providing (–)-brevianamide B (**38**) after the pinacol rearrangement. [24c]. While an enzyme would likely be needed to effect the oxidation to the opposite, more hindered α–face, leading to (+)-brevianamide A (**13**). When Williams *et al.*., synthesized tritium-labeled deoxybrevianamide E (**36**), and fed it to the *Penicillium brevicompactin*, they found clean and efficient incorporation of this label into both brevianamide A (**13**) and B (**12**) [25] (Scheme 9). This confirmed that deoxybrevianamide E (**36**) was at least a biosynthetic precursor; additionally, they found that there was high level of tritium label incorporated into the other product brevianamide E (**44**). They explored the possibility that brevianamide E (**44**) was a biosynthetic intermediate of brevianamide B (**12**) and brevianamide A (**13**). They converted ^{13}C deoxybrevianamide E (**36**) into brevianamide E (**44**) by photooxidation and reduction, but the subsequent feeding experiments showed no

incorporation into the isolated brevianamide A and B. They concluded that brevianamide E (**44**) was simply a shunt metabolite.

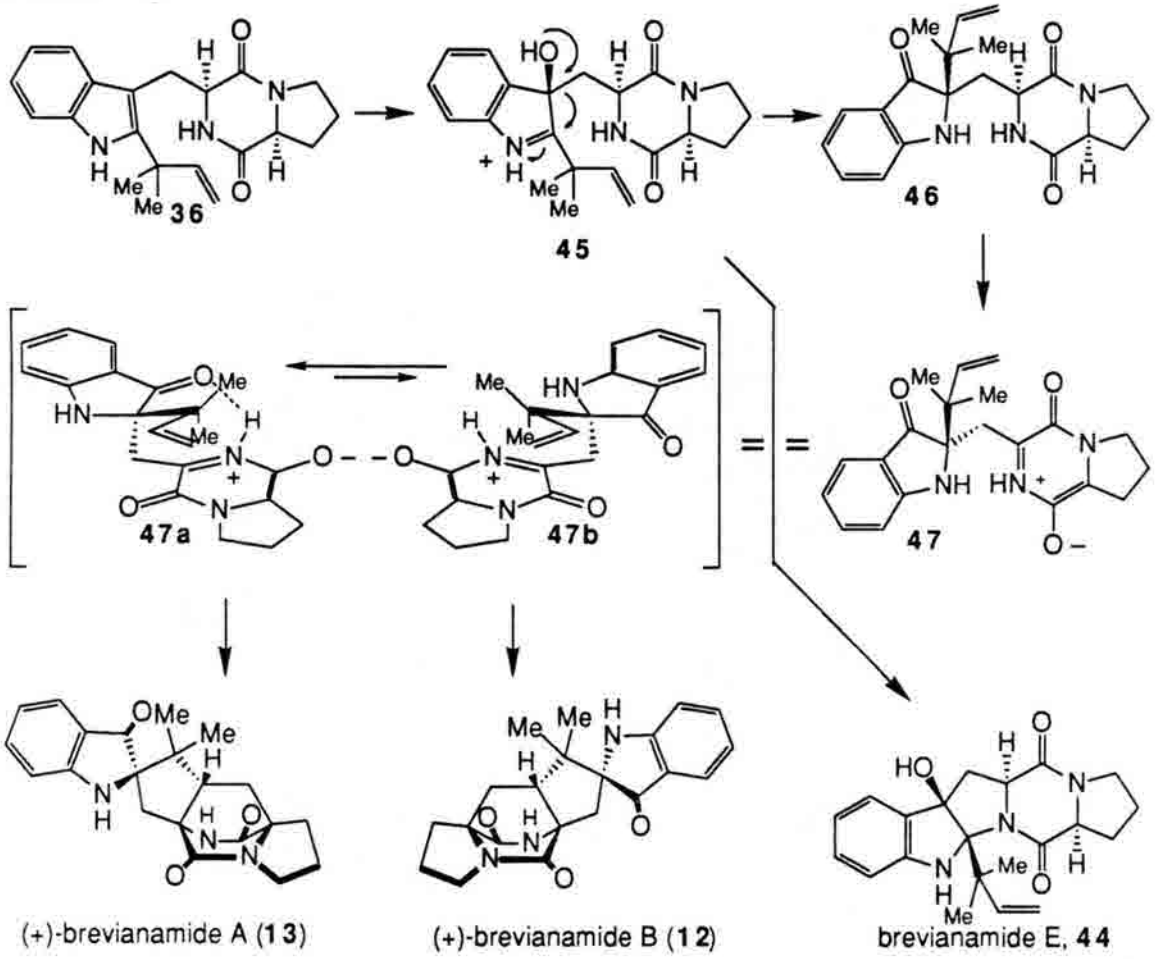
Scheme 9



These results led Williams to propose a modified mechanism (Scheme 10), in which the indole oxidation takes place first. The intermediate **45** forms in an R selective manner from **36**; it has already been shown experimentally that the photooxidation of deoxybrevianamide E (**36**) gives primarily **45** (a 2:1 ratio of the R vs S configuration)[26] . This tertiary alcohol (**45**) would undergo a pinacol-type rearrangement resulting in **46**, followed by a two-electron oxidation occurring in tandem with an enolization leaving **47**. At this point the molecule is set up for the proposed intramolecular Diels–Alder cyclization. Whether this reaction is enzyme catalyzed or not, remains to be seen. In any event, the relative amounts of the two products, brevianamide A (**13**) and brevianamide B (**12**) is

dependent upon the rotation of the bridging methylene bond and the face of cycloaddition. As Scheme 10 indicates rotamer **47a** leads to the major metabolite, brevianamide A (**13**), while **47b** leads to the minor product, brevianamide B (**12**).

Scheme 10



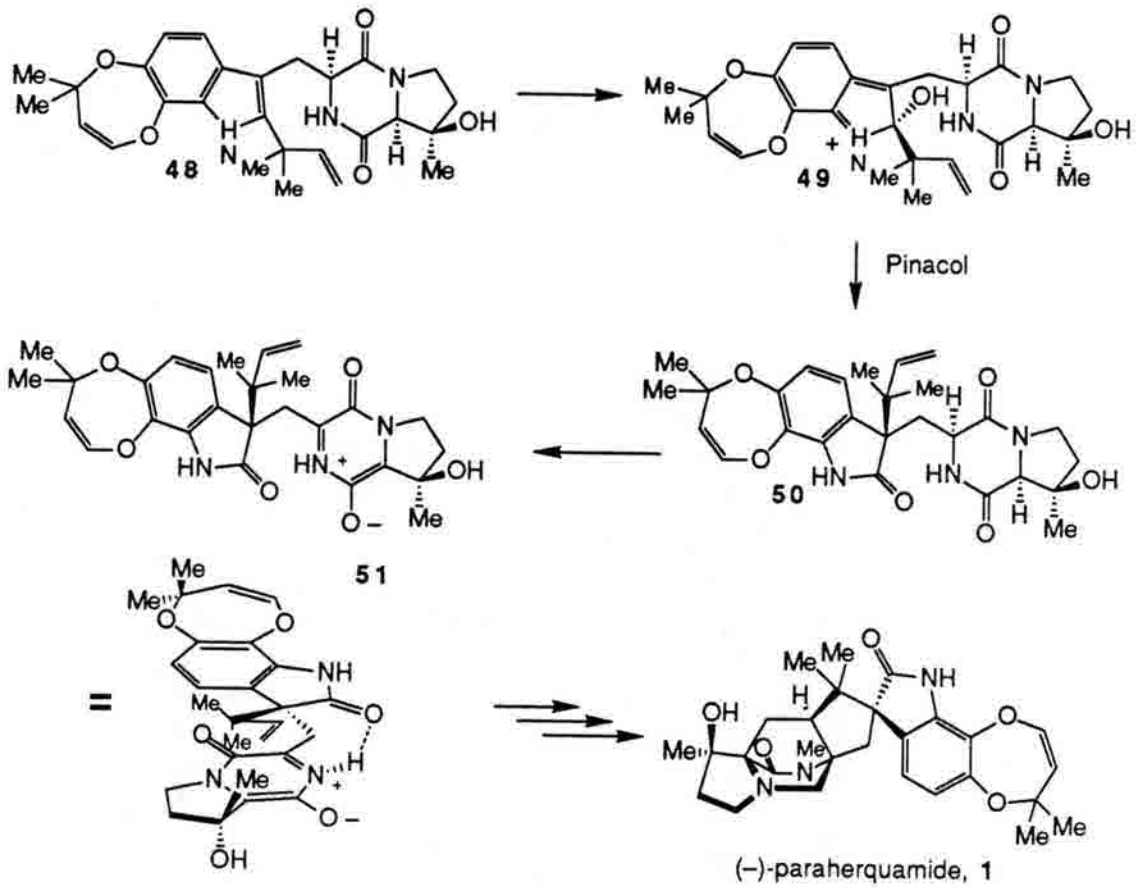
A molecular mechanics calculation showed that rotamer **47a** is one kcal lower in energy than rotamer **47b**. The increased stability was attributed to a hydrogen bond between the amide proton and the indoxyl carbonyl, which can only occur in rotamer **47a**. This refined proposal explains the formation of brevianamide E (**44**) and accounts for the enantiomeric [2.2.2] bicyclic ring system without invoking the hypothetical intermediates **40** and **41.** This proposal also accounts for the larger relative amounts of brevianamide B (**12**) compared to brevianamide A (**13**).

It is well known that in most Diels–Alder reactions, the ideal situation for spontaneous reactivity is to have either an electron rich diene and an electron poor dienophile, or an electron poor diene and an electron rich dienophile. In the present case, (**47**) the dioxopiperazine diene is quite electron rich while the dienophile is electron neutral. Therefore, it seems unlikely that the cycloaddition would occur spontaneously. Williams has proposed that to overcome this electronic barrier, an as yet unknown Diels–Alderase is responsible.[25] It seems reasonable that an enzyme would be required because no Diels–Alder intramolecular reaction is known that involves a piperazinedione and an electron rich dienophile; however, if this were the case it appears unlikely that the enzyme would allow a rotation (giving rotamer **47a** and **47b**) to take place. Williams has speculated that this diels alderase is in fact the same oxidase that converts **46** to **47.**

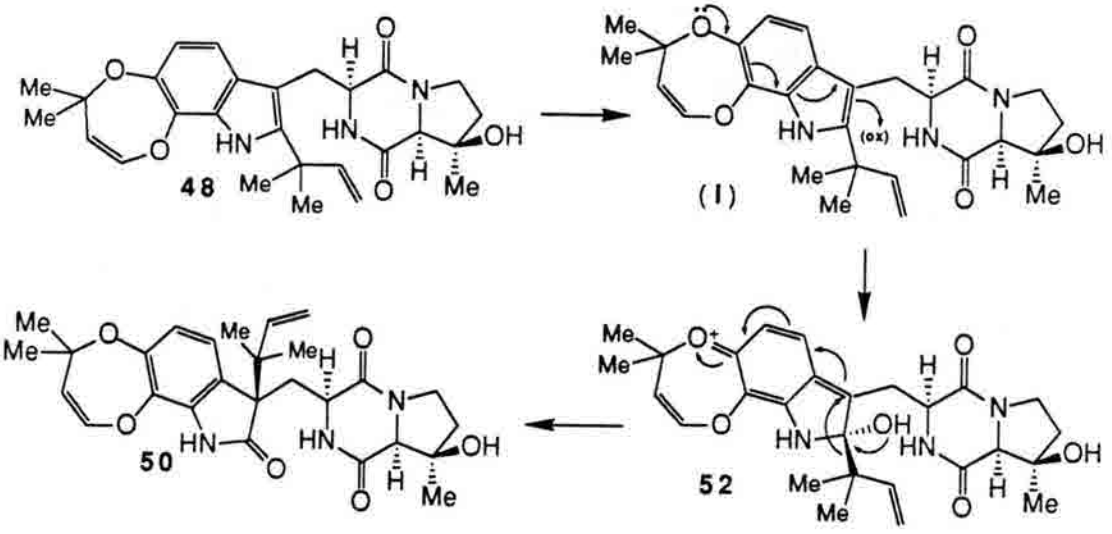
1.6 Implications for the Biosynthesis of the Paraherquamides and Marcfortines.

The basic biosynthetic pathway proposed by Williams can be invoked to explain the biosynthesis of both the paraherquamides and marcfortines (Scheme 11). As Scheme 11 indicates, the main difference between this mechanism and the one for the brevianamides takes place in the first step. In Scheme 10, deoxybrevianamide E (**36**) is first oxidized at the third position of the indole ring leading to the brevianamide indoxyl. This mirrors the known reactivity of indoles; in general the 3-position is the most reactive toward electrophiles. However, the paraherquamides and marcfortines are oxindoles, so the oxidation must take place at the 2-position of the indole ring. On the way to the synthesis of paraherquamide B (**3**), we have learned that the 2-position is very reactive relative to the 3-position. This is illustrated by the resonance structure **49** and **52.** It is the intermediacy of the oxonium that causes the increased reactivity at position 2 (Scheme 12). There is some experimental work that lends credence to this hypothesis (See chapter 3). In the course of our investigation of the cationic cyclization reaction from the S_N2' product **291**, it was discovered that the cyclization would not occur under strictly acidic conditions.

Scheme 11

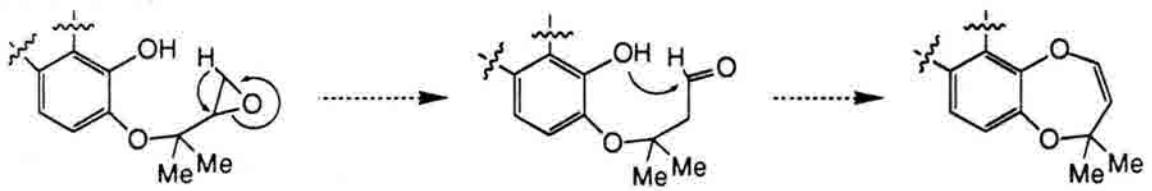


Scheme 12



This was contrary to the known reactivity of the brevianamide precursors, where the cyclization was smoothly effected by HCl in dioxane. From these results it was surmised that the indole at the two position was protonated before the *exo*-olefin. Additionally, the same kind of reactivity was encountered in the penultimate step of the paraherquamide B (**3**) synthesis. The oxonium hinders the pinacol type rearrangement of the chloroindolenine (see page 130). An inspection of Scheme 2 and 3 reveals that all the paraherquamides and marcfortines contain the required phenolic ether that leads to the oxonium intermediate. Most of these are dioxepins like paraherquamide itself, but a few are pyrans (paraherquamides F, G and marcfortine C). In these three cases, the phenyl ether is in the 6-position as required by the mechanism outlined above. Obviously, there are some major differences between the biosynthesis of the brevianamides and the paraherquamides. The structural differences were mentioned previously, but it is reasonable that the basic 6,7-dioxy-indole moiety is formed fairly early in the biosynthesis of these molecules, most likely from an air-oxygenated form of tryptophan. A mechanism for the dioxepin ring formation was proposed. Polonsky [8] envisioned a reaction between the oxygenated tryptophan and a dimethylallyl–pyrophosphate. The olefin would become epoxidized, undergo a 1,2-hydride shift to the aldehyde, and intramolecularly condense with the required phenol (Scheme 13).

Scheme 13



At some point, the amide carbonyl would be reduced [10] and the secondary amide N-methylated. The former process was mentioned previously and the latter is greatly precedented.[27] It is interesting to note that both marcfortine B and C lack this N-methylated moiety, implying that the N-methylation step occurs later in the overall biosynthesis.

1.7 Pharmocology

Originally, paraherquamide was tested on a simple animal model (gerbils). The results showed paraherquamide A (**1**) has strong activity against a benzimidazole- and avermectin-resistant helminth (*Trichustiogylus colubriformis*). Paraherquamide A (**1**) was well tolerated by the gerbils even at a high dose (200mg kg^{-1}) [5] (Table 1).

Table 1

Efficacy of paraherquamide against immature *Trichstrongylus colubriformis* in gerbils and a comparison to some other anthelmintics.[5,28]

treatment	dosage mg kg^{-1}	number of animals	efficacy %
placebo	-	8	-
paraherquamide	200	3	100
	100	3	100
	50	3	100
	6.25	5	100
	3.12	4	99.7
	1.56	3	98.1
	0.78	3	96.5
	0.39	3	66.3
thiabendazole	200	3–6	85
	100	3–6	72.3
	50	3–6	44.1
levamisole hydrochloride	6.25	3–6	100
	3.125	3–6	80.3
	1.562	3–6	40.7
avermectin A_1a	0.125	3–6	99.4
	0.0625	3–6	79.3
	0.0312	3–6	57.4
avermectin A_2a	0.125	3–6	99.8
	0.0625	3–6	90.1
	0.0312	3–6	55.9
avermectin B_1a	0.0312	3–6	100
	0.0156	3–6	75.4
	0.0078	3–6	18.8
avermectin B_2a	0.0312	3–6	100
	0.0156	3–6	95
	0.0078	3–6	75.7

A subsequent animal study was performed on various nematode-infected sheep.[6a] Seven different species, larval and adult, were presented to the sheep including an Ivermectin-resistant strain (*Haemochus contortus*) and an Ivermectin/benzimidazole-resistant strain

(*Trichostrongylus colubriformis*). Paraherquamide A (**1**) showed good activity against these, in doses ranging from 2.00–0.25 mg of paraherquamide per kg of sheep body weight. In almost all cases the efficacy was 99% or greater; however, **1** was ineffective against *Oesophagostomum columbianum* (zero percent efficacy at the 0.25 mg kg^{-1} level). Another study demonstrated the safety and efficacy of paraherquamide on cattle.[29] Calves were infected with nine different species of nematode larvae and then treated with Paraherquamide at doses ranging from 4mg kg^{-1} to 0.5mg kg^{-1}. The only nematode that was not well affected was *C punctata* (zero percent efficacy at the 0.5 mg kg^{-1} level). The other eight were killed with >95% efficacy at the 1.0mg kg^{-1} level. It was reported that the calves suffered no ill effects. Problems arose when **1** was fed to dogs at doses much lower than those used on calves and sheep. The mixed breed dogs showed acute toxicity reactions.[30]; because of this, a toxicity profile was undertaken comparing Paraherquamide A (**1**) to ivermectin using mice as the animal vector.[31] It was concluded that not only is paraherquamide more toxic than ivermectin but it has a different mode of toxicity. The mice fed paraherquamide A suffered respiratory distress followed by death. In contrast, mice fed ivermectin suffered ataxia, coma and then death.

A Merck group performed a study [32] that reported a membrane binding site of paraherquamide A (**1**) and a membrane preparation from *Caenorhabditis elegans*. This was done by synthesizing [^{3}H] paraherquamide (^{3}H incorporated at position 24) [33] and incubating it with membranes obtained from macerated *C. elegan* worms. A Scatchard plot analysis of the binding data pointed to one particular high affinity binding site for paraherquamide. The dissociation constant K_d = 263μM was found that compared favorably with 268μM obtained from a kinetic binding study. This value $k_{-1}/k_1 = K_d$ was found by examining the effect of excess unlabeled paraherquamide A (**1**) incubated with the ^{3}H paraherquamide A membrane complex and measuring the rate of decline of the [^{3}H]paraherquamide over time (giving k_{-1} = 1.1min^{-1}). The specificity of paraherquamide to this binding site was also examined. Various analogs of paraherquamide were tested to

see how well they inhibited paraherquamide binding. While none of the analogs bound as strongly to this site as paraherquamide itself, they did find an almost one–to–one correlation between binding and a motility assay (Ec50 ug/mL) for *C.elegans*, indicating that this binding site is indeed the active site for biological activity. Another experiment was done to find out if the membrane binding site of paraherquamide is the same for other anthelmintic agents. While all of the compounds tested showed antinematode activity, only the phenothiazine analogs had any specific inhibitory effects at the paraherquamide binding site. This was an interesting result indicating both types of compounds interact at a common or close binding site. The mode of action of phenothiazine is not known, though it does possess both anthelmentic and antiprotozoal activity. The Merck group concluded that paraherquamide interacts (interferes) with a specific ligand–receptor that could be the same as for the phenothiazines. The nature of this site remains to be determined.

The Merck group did much synthetic work in modifying paraherquamide. They reported making over 100 different analogs of this compound[32]. Unfortunately paraherquamide seems to be the most active. Additionally, of the natural paraherquamides, paraherquamide A (**1**) is the most active (Table 2)

Table 2

Antinematodal activity of the natural paraherquamides against *C. elegans*.

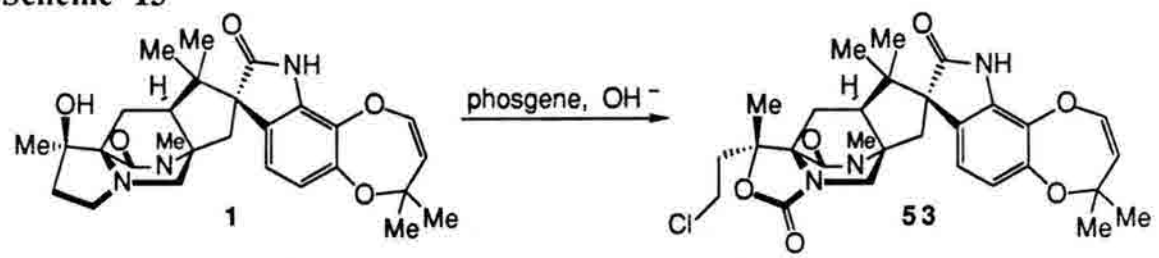
compound	LD_{50} (μg/mL)
(–)-paraherquamide A (**1**)	2.5
(–)-paraherquamide B (**2**)	100
(–)-paraherquamide C (**4**)	40
(–)-paraherquamide D (**5**)	160
(–)-paraherquamide E (**6**)	6
(–)-paraherquamide F (**7**)	65
(–)-paraherquamide G (**8**)	20

1.8 Semi-Synthetic Studies

Even though the biological activity of paraherquamide A (**1**) could not be improved, a great deal of interesting chemistry was discovered. Initial efforts involved the

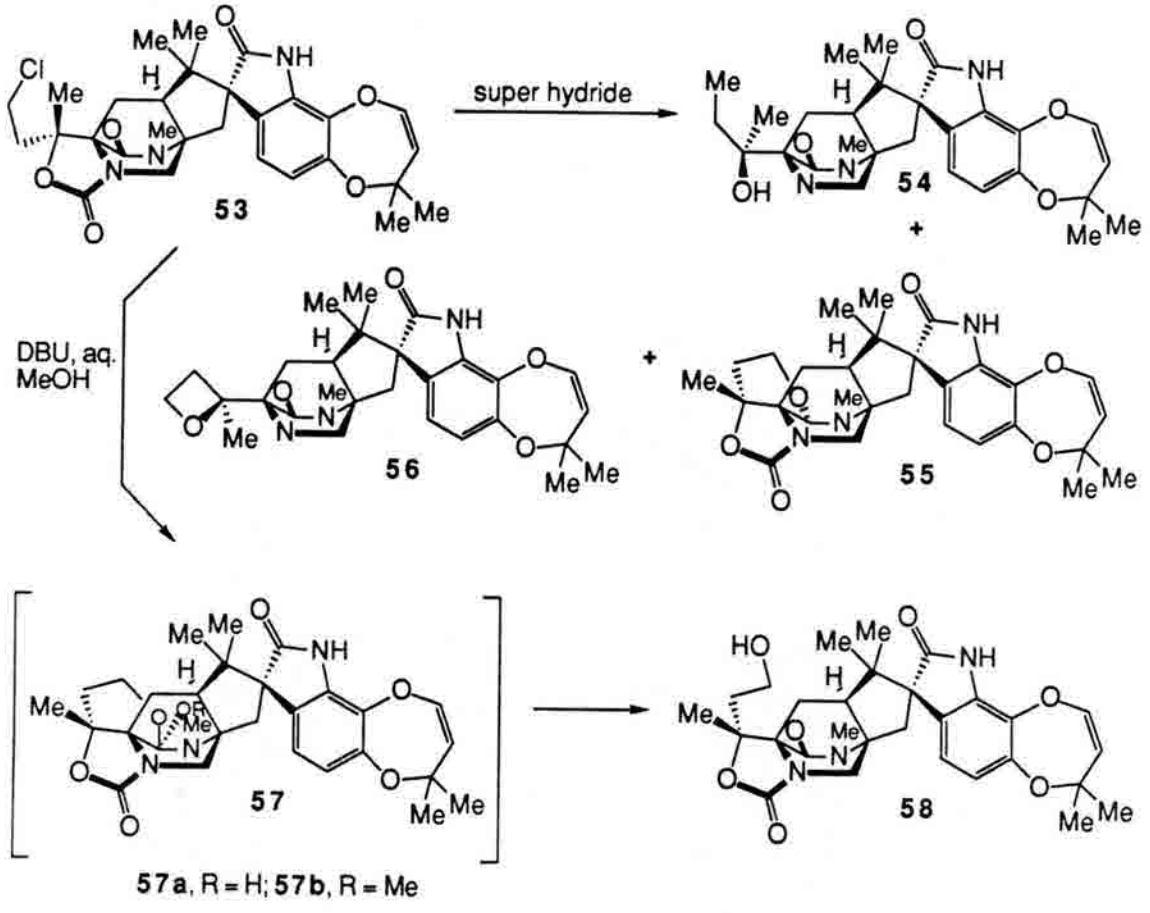
modification of the C-14 position of paraherquamide A. (**1**). Blizzard et al [2], treated **1** with phosgene and methanol, expecting to obtain the methyl carbonate, but instead they formed some unusual by-product. By modifying this reaction slightly, using base instead of methanol, the product isolated was a cyclic urethane **53** (Scheme 13).

Scheme 13

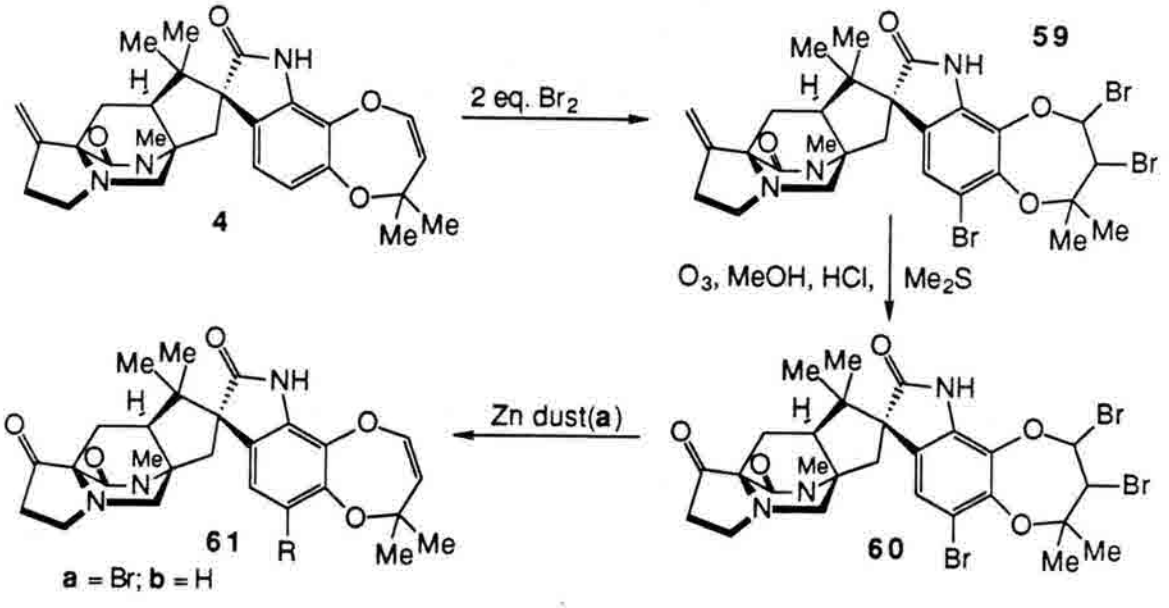


They thought that the initially formed chloro-ester closed on the tertiary amine giving a quaternary salt. The free chloride ion then attacked the C-16 methylene opening the proline ring. This unexpected product was subsequently treated with super hydride in an attempt to reduce off the chloride. Surprisingly, this reaction produced three unanticipated products, but no trace of the desired propyl compound (Scheme 10). The chloride was cleanly hydrolyzed to the alcohol **58** with aq DBU in methanol. They stated that it probably went by way of cyclic intermediate **57a**. This mechanism seems reasonable, because the acetal **57b** was isolated when **53** was treated with sodium methoxide in methanol (Scheme 15). This unusual reactivity of the proline end of the molecule could not be duplicated on the oxindole portion of the molecule.

Scheme 15

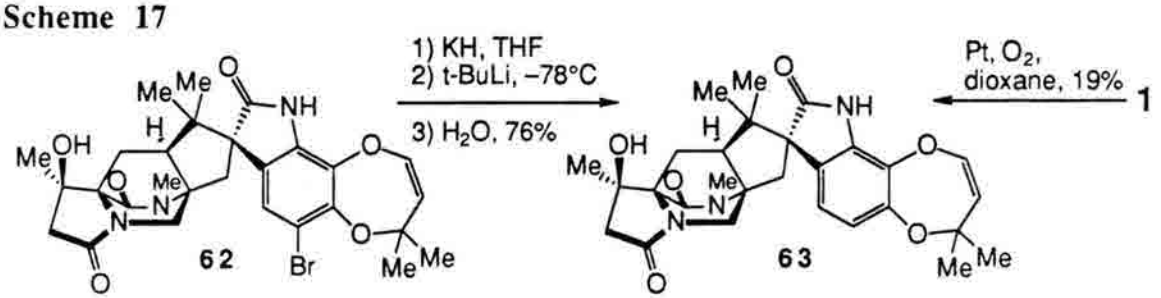


Scheme 16



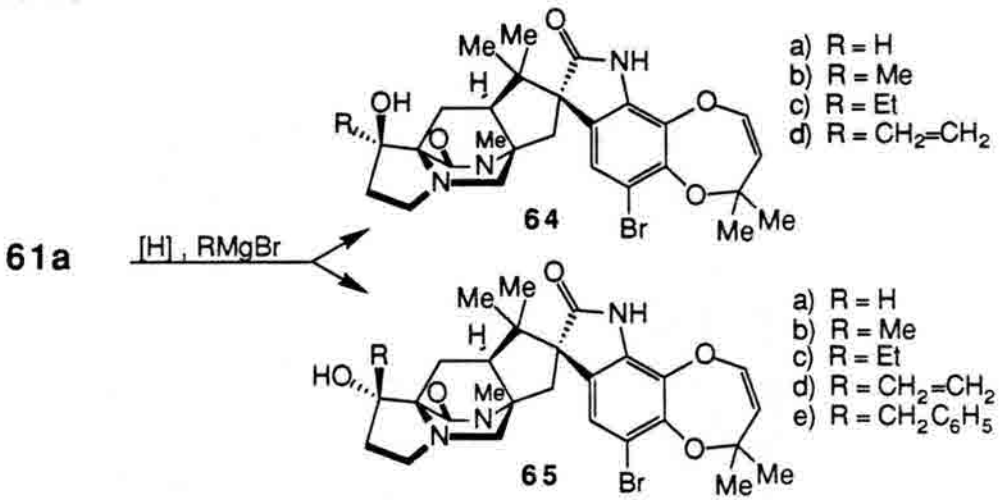
When **1** was N-alkylated with 1-bromo-3-chloropropane and then subjected to the same reduction conditions (super hydride) only the normal 1-N-propyl paraherquamide was formed. The difference was attributed to the close proximity of the lactam carbonyl of **53** to the propyl chloride, while there is little constraint placed upon the 1-N-3-chloropropyl moiety, with a greater field of rotation. The Merck group did many other experiments involving the proline portion of the molecule.[35] An attempt to convert the tertiary alcohol of **1** to a fluoride with DAST{(diethylamino)sulfur trifluoride} gave primarily the *exo*-methylene, paraherquamide C (**4**). The conversion of this olefin to a ketone proved difficult; apparently, the phenyl ring was easily oxidized in the presence of ozone. The problem was with 5-position of the oxindole ring. To overcome this, the Merck group had to treat **4** with two equivalents of bromine, blocking this position and the sensitive dioxepin olefin. This provided them with the tribromide **59** that was effectively converted to the ketone **60**. The *vic*-dibromides were then removed with zinc dust to provide **61a** in 26–36% yield from **4**. If only one equivalent of bromine was used on **4**, the yield of the ketone **61b** was only 5%. The bromine of **61a** was removed by a halogen metal exchange providing them with **61b** (Scheme 16). Interestingly, if paraherquamide A (**1**) was treated with four equivalents of bromine followed by zinc reduction, the resulting product was the 16-oxo-5-bromo derivative **62**. To confirm this structure, the bromine was removed by halogen metal exchange. This product (**63**) was compared to the same 16-oxo-derivative which was synthesized by the platinum catalyzed oxidation of paraherquamide A (**1**) (Scheme 17).[2]

Scheme 17



The ketone **61a** proved useful for effecting various changes in the C-14 portion of the molecule. It was reduced with LAH to give a 40:60 mixture of **60a** and **65a**; however when the same substrate was treated with sodium borohydride only the epimeric alcohol **65a** was produced. The ketone **61a** was also treated with numerous Grignard reagents (b-e) (Scheme 18)[34].

Scheme 18



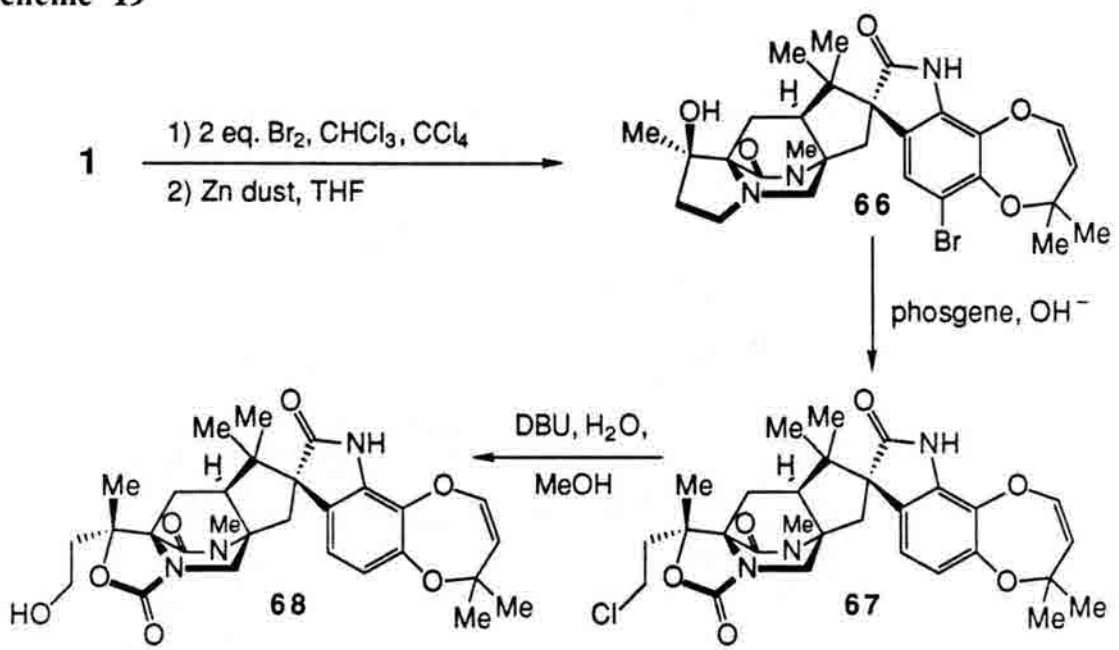
Interestingly, the selectivity varied widely. When **61a** was treated with methyl magnesium bromide the ratio of **64b** to **65b** was 1:2; however, ethyl magnesium bromide gave a 3:1 ratio of **64c** and **65c**. A reaction of vinyl magnesium bromide with **61a** left only one product, the natural epimer **64d**; in contrast, benzyl magnesium chloride reacting with **61a** produced the unnatural epimer **65e**. The explanation given for this remarkable difference in reactivity was that there were different states of aggregation or complexation between the amide carbonyl and metal cation. All these 5-bromo-derivatives were debrominated by treatment with t-butyl lithium, and quenching with water.

1.9 The Absolute Configuration of Paraherquamide A

The Merck group set out to determine the absolute configuration of paraherquamide, but they found that none of the previously mentioned brominated derivatives proved crystallizable. They treated 5-bromo-paraherquamide **66** with phosgene resulting in the oxazolidinone **67**, which was then converted to the alcohol **68**. This

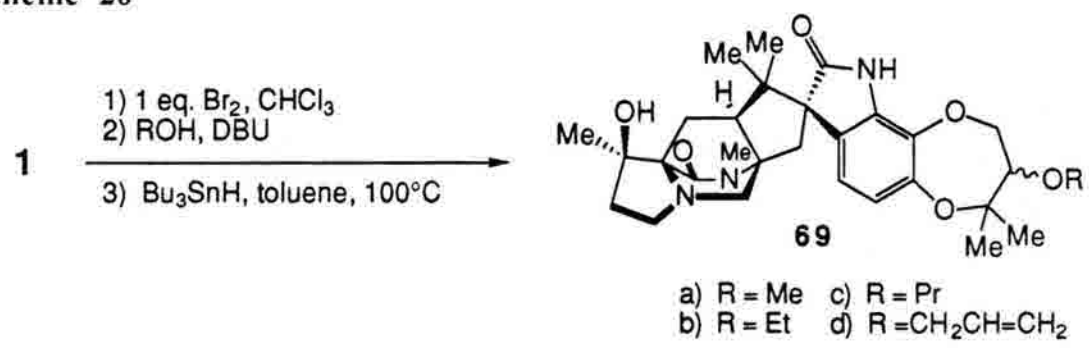
material was crystalline, and an x-ray diffraction pattern was obtained. Due to the heavy atom, the absolute configuration was firmly established, [2] which in turn unequivocally established the absolute configuration of (–)-paraherquamide A (**1**) (Scheme shown).

Scheme 19



The dioxepino portion of the molecule was also modified.[35] Starting with the *vic*-dibromide, a number of alkoxy bromides could be generated. Treatment of the dibromide with tri-butyltinhydride in the presence of an alcohol gave the corresponding acetals (**69**) (Scheme 20).

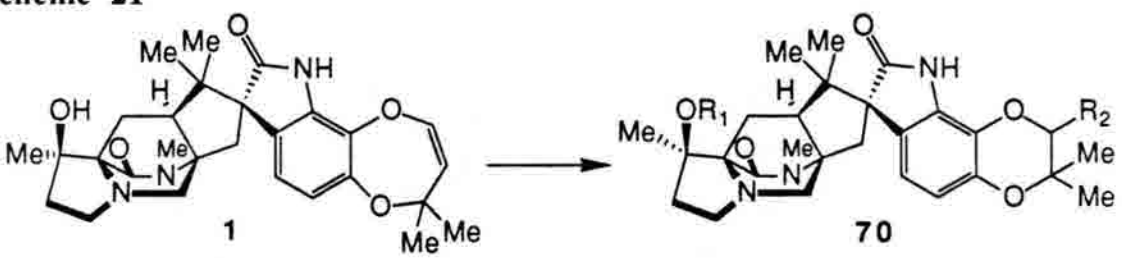
Scheme 20



The dioxepin portion of **1** was converted to the six-membered ring acetal **70a** by treating an acidic solution of paraherquamide with ozone (O_3, 9:1 methanol/1N HCl, Me_2S, 66%). It was imperative that the solution be made acidic because the tertiary amine

was thought to be oxidized in the absence of acid. Paraherquamide A was also subjected to 20 equivalents of BSTFA{bis(trimethylsilyl)trifluoroacetamide} in dimethylformamide at 25 °C for twenty-six hours yielding the O-silyl-protected tertiary alcohol in 93%. This was treated with ozone in acidic medium to give **70b** in 67% yield, which was converted to a diastereomeric mixture of fluorides **70c** with six equivalents of DAST (diethylaminosulfur trifluoride) in chloroform (76%). The two resulting diastereomers were separated and treated (HF/pyridine/THF) giving **70d**, with a combined yield of 84% (Scheme 21).

Scheme 21

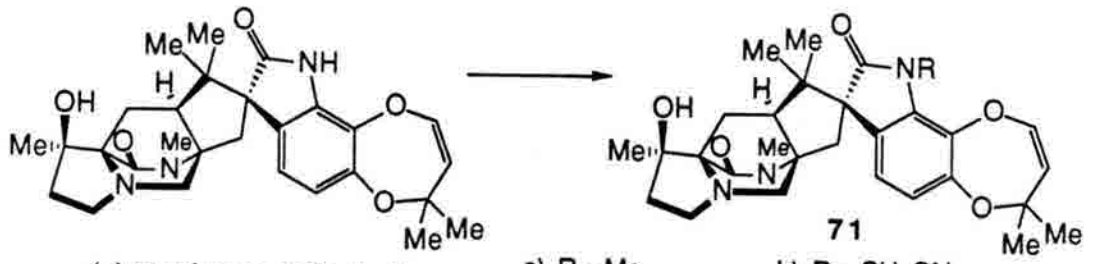


a) $R_1 = H, R_2 = OH$, c) $R_1 = TMS, R_2 = F$
b) $R_1 = TMS, R_2 = OH$ d) $R_1 = H, R_2 = F$

The other portion of paraherquamide that was extensively modified was the amido oxindole.[36] Various N-alkylated and N-acylated compounds were prepared for biological testing. The alkylations were generally carried out with an excess of KH followed by an excess of the alkylating agent. They reported that the alkylations could be controlled so that only very small amounts of the O-alkylated products were produced. When **1** was treated with a large excess of potassium hydride and ten equivalents of methyl iodide, the N-alkylated oxindole **71a** was obtained in 65% yield, with only small amounts of the bis-alkylated material. Similar effects and yields were found with the other alkylating agents (Scheme 22).

Paraherquamide A (**1**) was also extensively acylated. The Merck group found that the oxindole amide could be preferentially acylated or sulfonylated in the presence of the tertiary alcohol. When a tetrahydrofuran solution of **1** and excess KH was treated with acetic anhydride (11 eq) for 21h, **47a** was obtained almost exclusively (Scheme 23).

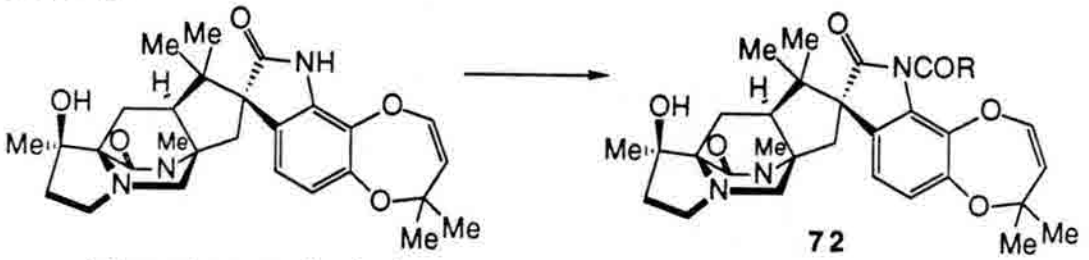
Scheme 22



(–)-paraherquamide A, **1**

a) R = Me
b) R = CH_2CN
c) R = CH_2SCH_3
d) R = $CH_2OCH_2CH_2OCH_3$
e) R = $CH_2C_6H_5$
f) R = $CH_2C_6H_5$-(pCl)

Scheme 23

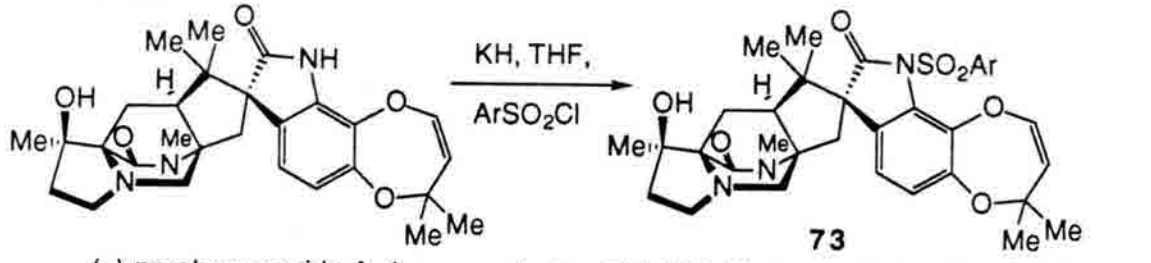


(–)-paraherquamide A, **1**

a) R = Me, 74%
b) R = CH_2OCH_3, 22%
c) R = C_6H_5, 24%
d) R = OCH_3, 78%
e) R = $N(CH_3)_2$, 93%
f) R = NHC_6H_5, 96%

Phenyl isocyanate reacted in a similar way. Paraherquamide A (**1**) and an excess of KH gave again primarily the urethane **72f**. Indeed in all these cases, both an excess of KH and the acylating agent was needed. Essentially the same reactivity was reported when **1** was sulfonylated under the same general conditions. It appears that the tertiary alcohol of **1** is quite unreactive toward most electrophiles except perhaps BSTFA (Scheme 24).

Scheme 24



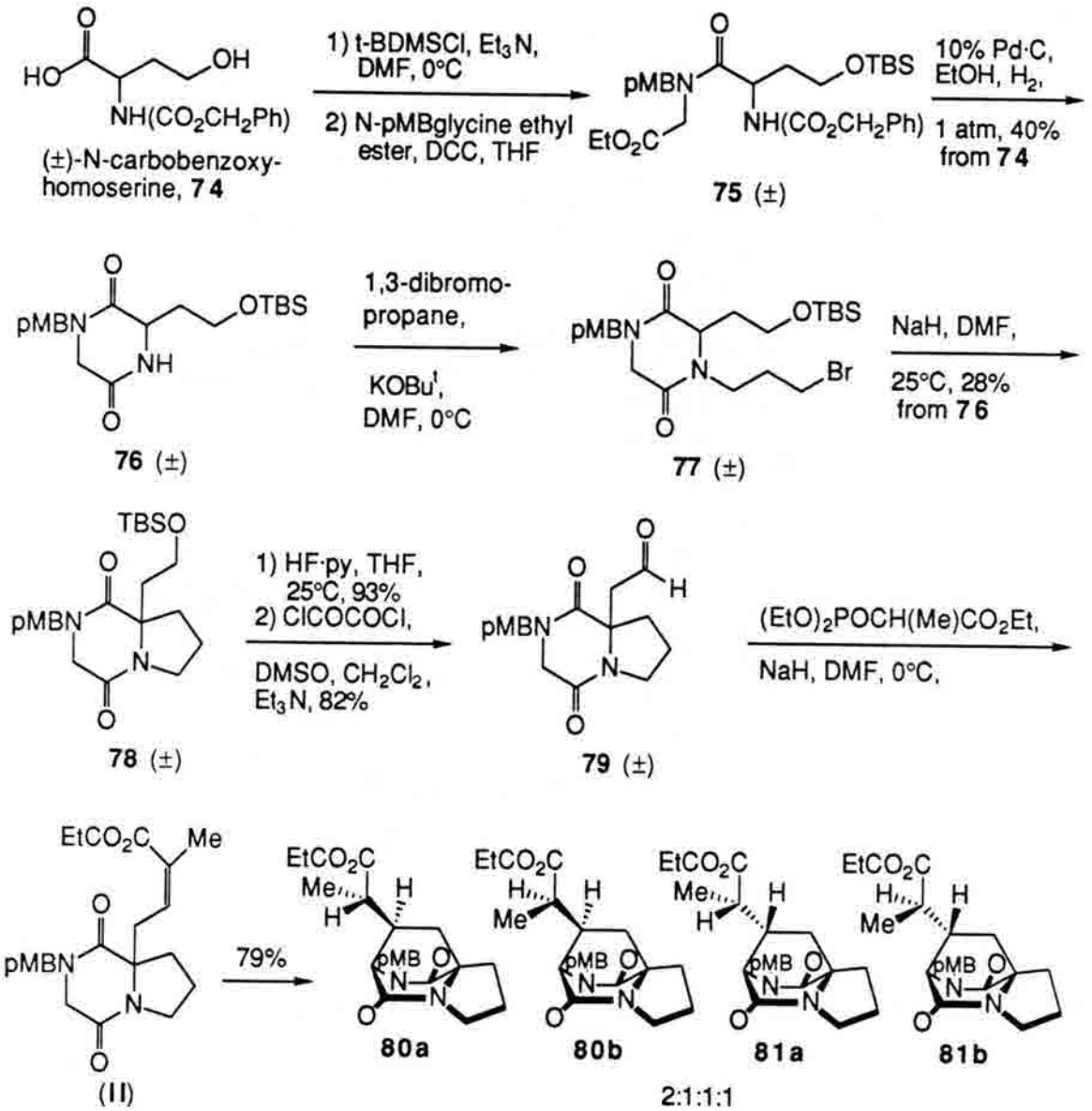
(–)-paraherquamide A, **1**

a) Ar = Ph(pMe), 61%
b) Ar = Ph(pBr), 73%
c) Ar = Ph(oNO_2), 33%
d) Ar = Ph(pOMe), 89%

1.10 The Total Synthesis of (–)-Brevianamide B (38)

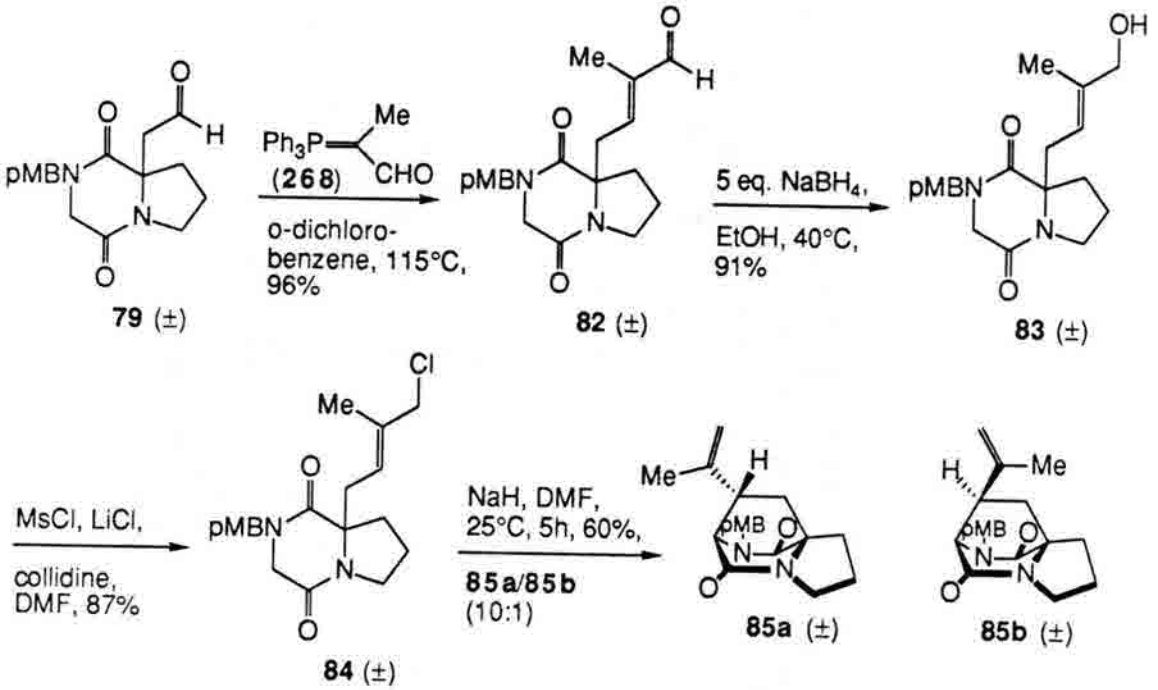
The early efforts of Williams and coworkers [24a] led to the construction of the tricyclic skeleton of brevianamide B (Scheme 25). This initial approach would later serve as a useful model for the total synthesis. (±)-Carbobenzoxy homoserine (**74**) was silylated and condensed with N-*para*-methoxybenzylglycine ethyl ester to provide protected **75**. This product was subjected to hydrogenolysis giving them the piperazinedione **76**. This material was then alkylated with 1,3-dibromopropane to afford **77**, and was immediately cyclized to provide the required proline **78**. Desilylation and oxidation of **78** gave the aldehyde **79**, which was homologated with $(EtO)_2POCH(CH_3)CO_2Et$, spontaneously cyclizing to the desired tricyclic products (**80a,b** & **81a,b**). The structure of the major isomer was established by X-ray crystallography and was found to have the unnatural stereochemistry.

Scheme 25


1) t-BDMSCl, Et3N, DMF, 0°C
2) N-pMBglycine ethyl ester, DCC, THF
10% Pd·C, EtOH, H2,
1 atm, 40% from 74
(±)-N-carbobenzoxy-homoserine, 74
75 (±)
1,3-dibromo-propane,
KOBut, DMF, 0°C
NaH, DMF,
25°C, 28% from 76
76 (±)
77 (±)
1) HF·py, THF, 25°C, 93%
2) ClCOCOCl,
DMSO, CH2Cl2, Et3N, 82%
(EtO)2POCH(Me)CO2Et,
NaH, DMF, 0°C,
78 (±)
79 (±)
79%
(11)
80a
80b
81a
81b
2:1:1:1

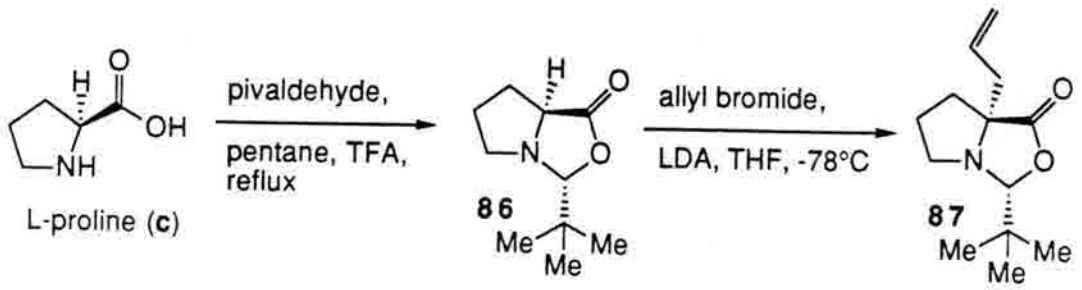
A slightly more successful approach involved the homologation of **79** with $Ph_3P{=}C(CH_3)CHO$. This reaction gave the E olefin **82**, which was reduced to the alcohol **83**, and converted to the allylic chloride **84.**[38] The chloride was cyclized with sodium hydride in dimethylformamide to provide the olefins **85a, b** in a 10:1 ratio. The tricyclic product **85a** had the desired stereochemistry [24a] (Scheme 26).

Scheme 26



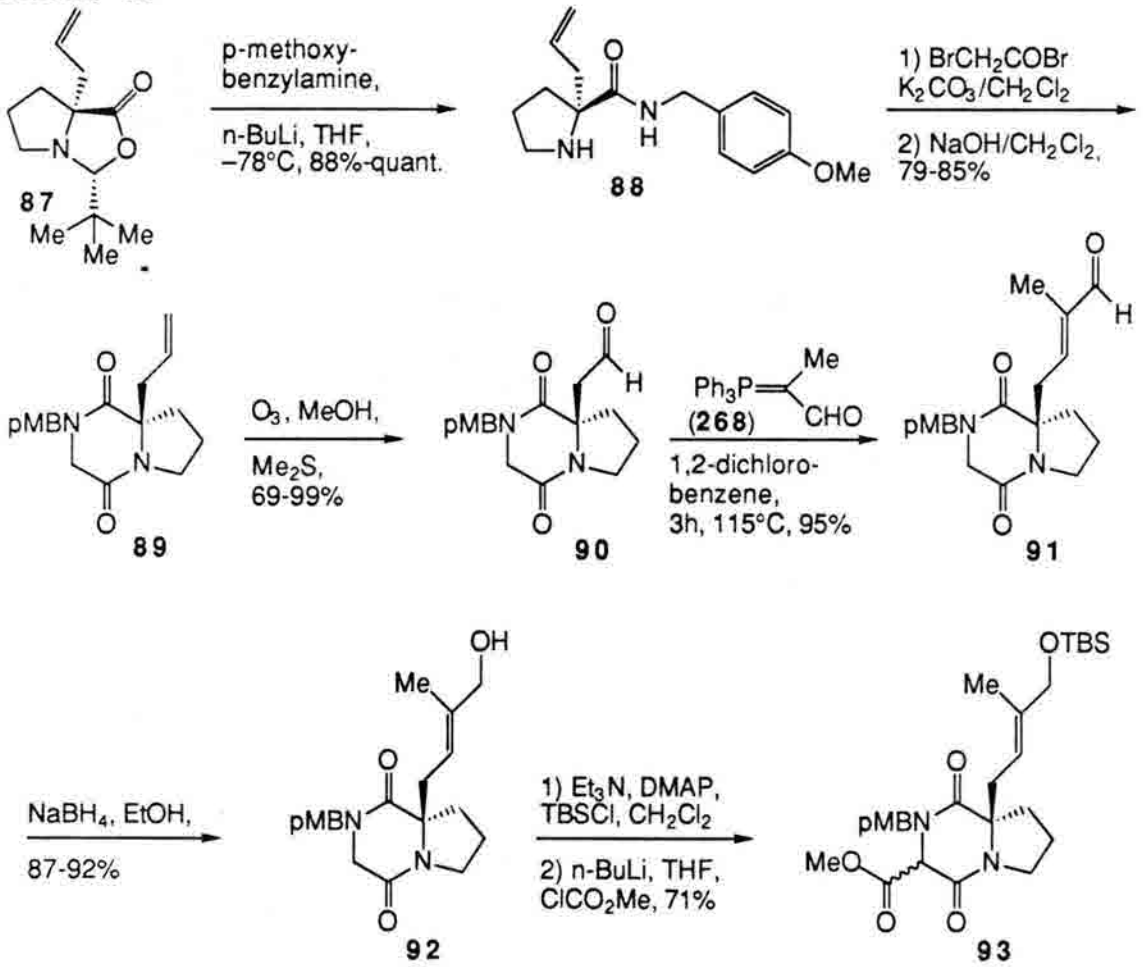
In 1988 Williams *et al.* [24b, c] completed the total synthesis of (–)-brevianamide B in 20 steps from L-proline. The synthesis incorporated the procedure of Seebach.[38] Proline is condensed with pivaldehyde and then stereospecifically alkylated with an alkylating agent, in this case allyl bromide (Scheme 27).

Scheme 27

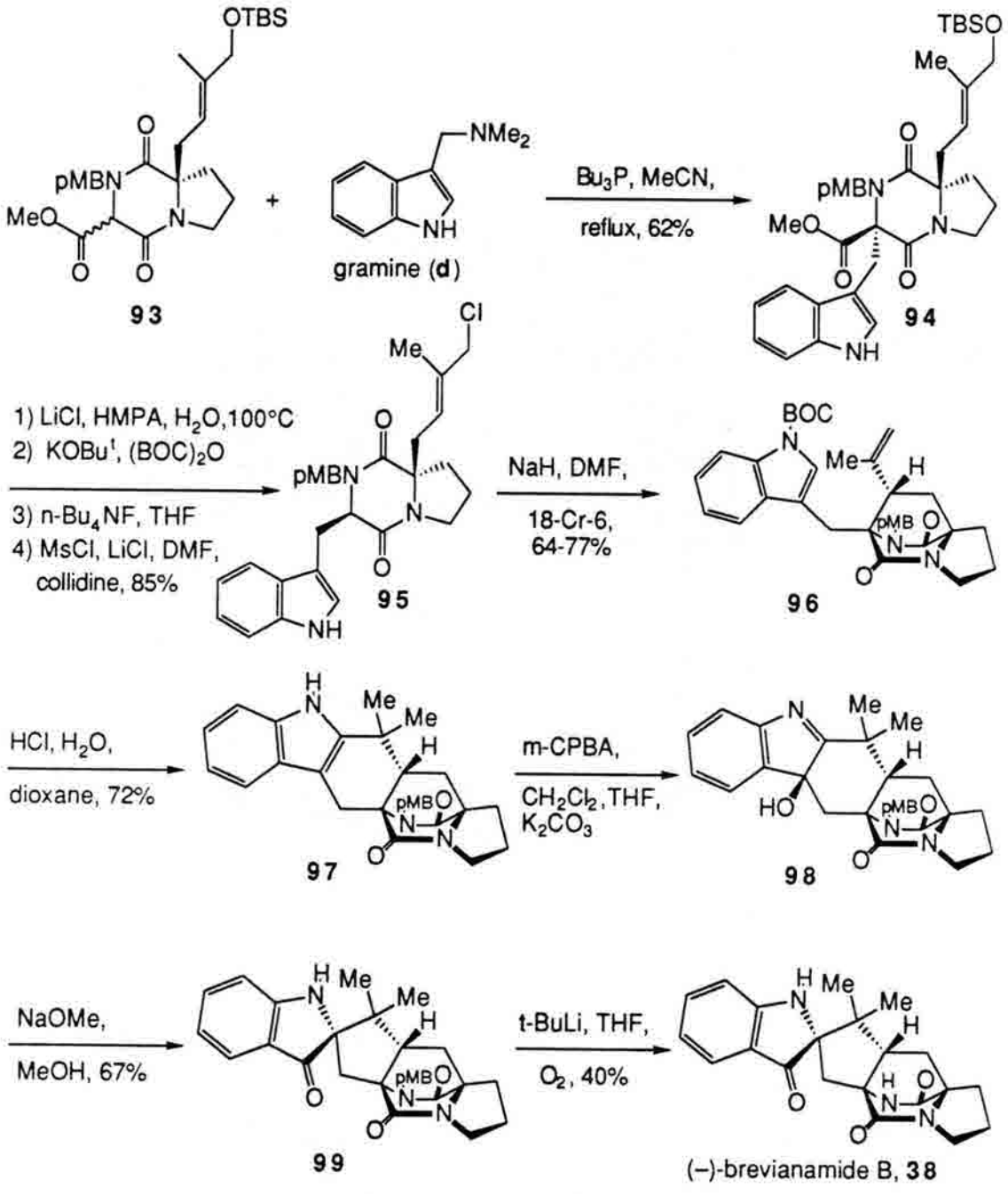


The heterocycle **87** was treated with preformed *para*-methoxybenzylamide anion (n-BuLi, p-methoxybenzylamine, THF, –78 °C) giving the the amide **88** in 88% to quantitative yield. Acylation of **88** with bromoacetyl bromide and K_2CO_3 followed by ring closure onto the amide with aqueous NaOH left the piperazinedione **89** in 79–85% yield. This two step–one pot procedure was followed by an ozonolysis that after dimethyl sulfide workup gave the aldehyde **90** (the chiral version of **79**) in 69–99% yield. This aldehyde **90** was homologated with $Ph_3PC(Me)CHO$ in 1,2-dichlorobenzene (3h, 115 °C) providing the enal **91** (the chiral version of **82**), which was reduced with $NaBH_4$ giving the alcohol **92** in 87–92% yield. This alcohol was protected with *tert*-butyldimethylsilyl chloride and acylated with methyl chloroformate to give **93** in 71% yield as an inseparable mixture of epimers; 4:1 (*syn/antri*) (Scheme 28).

Scheme 28



Scheme 29


OTBS
pMBN
MeO
93
gramine (d)
NMe2
NH
Bu3P, MeCN,
reflux, 62%
TBSO
Me
94
1) LiCl, HMPA, H2O,100°C
2) KOBu^t, (BOC)2O
3) n-Bu4NF, THF
4) MsCl, LiCl, DMF,
collidine, 85%
Cl
95
NaH, DMF,
18-Cr-6,
64-77%
BOC
96
HCl, H2O,
dioxane, 72%
97
m-CPBA,
CH2Cl2, THF,
K2CO3
HO
98
NaOMe,
MeOH, 67%
99
t-BuLi, THF,
O2, 40%
(–)-brevianamide B, 38

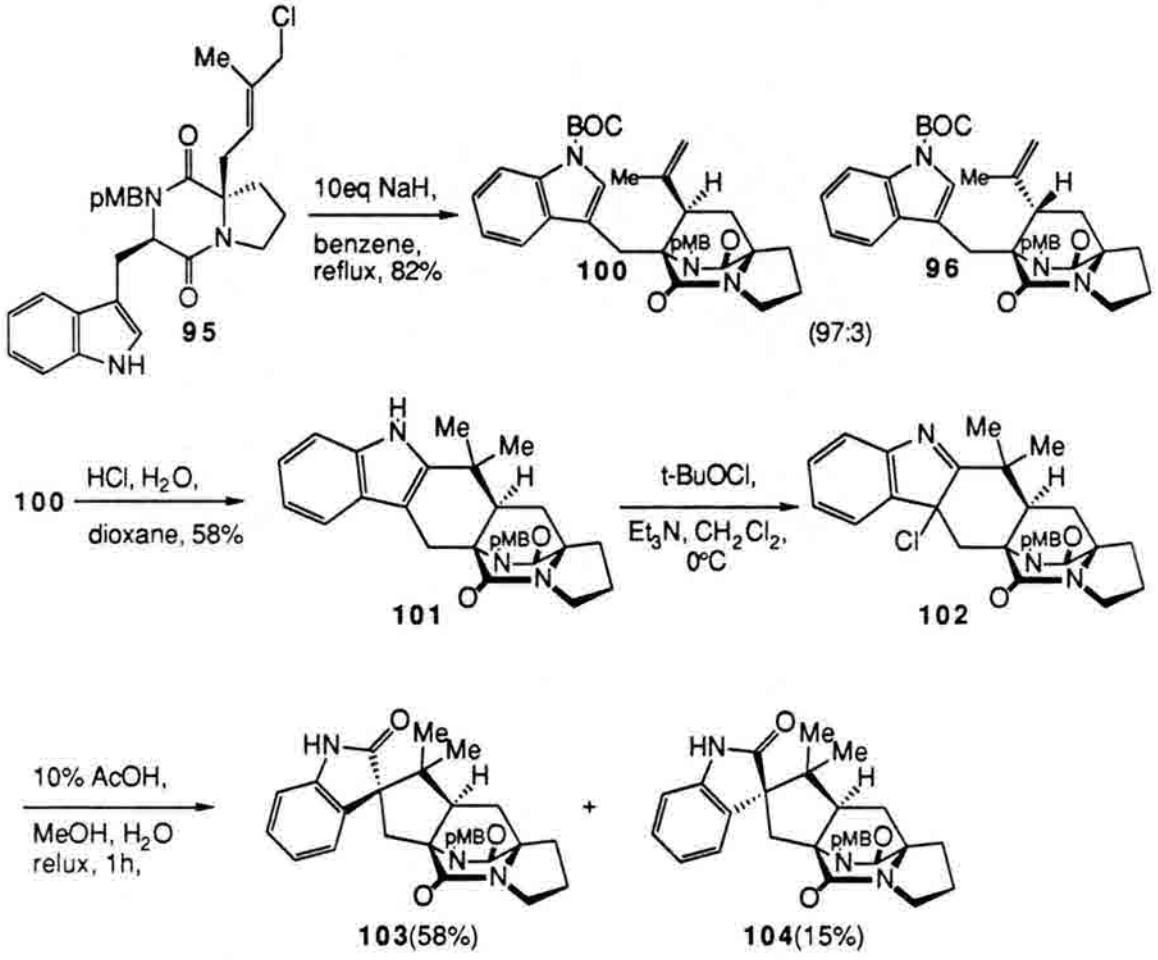
The diketopiperazine **93** was condensed with gramine in the presence of 0.4 equivalents of tributylphosphine to provide the indole **94** in 62% yield; interestingly, there was only one diastereomer *(syn)* formed during this reaction. Presumably the indole could only approach from the less hindered face of the molecule. This is also in agreement with the mechanism put forth by Somei.[39] The indole **94** was treated with LiCl in wet HMPA (hexamethylphosphoramide) to effect the decarbomethoxylation. The yield of this reaction was 88% (78% *syn*, 10% *anti* or approx. 8:1). Only the *syn*-isomer was used in subsequent steps. The indole was protected, and desilylated and then converted to the chloride **95** (MsCl, LiCl, collidine, DMF) in 85% yield from **94**. This indole **95** was subjected to the best cyclization conditions (sodium hydride, THF, 18-Cr-6,reflux) to deliver **96** in a ratio of 4.9:1 and 64% yield. With concentrated HCl in dioxane, **96** was cleanly transformed to the hexacyclic indole **97** with the concomitant loss of the *tert*-butoxycarbonyl protecting group. This carbocycle was then oxidized (m-CPBA in CH_2Cl_2/THF and K_2CO_3) to render the 3-hydroxyindolinine **98**. This material was immediately treated with sodium methoxide in methanol to effect the pinacol rearrangement, in an entirely stereoselective manner leaving the required indoxyl **99**. Deblocking the *para*-methoxybenzyl group of **99** proved difficult. After much experimentation it was finally removed with *tert*-butyl lithium and oxygen [40] awarding (–)-brevianamide B (**38**) in 40% yield (Scheme 29).

1.11 The Synthetic Strategy for (–)-Paraherquamide A (1)

The synthesis of paraherquamide A (**1**) was envisioned to take advantage of the key carbon–carbon bond forming steps of the brevianamide synthesis. These include the Somei/Kamatani coupling, the S_N2' reaction, the carbocationic cyclization, and the final oxidative spiro-cyclization. The paraherquamide A (**1**) synthesis would diverge from the brevianamide protocol because of its greater complexity, but the general framework would remain the same.

In the course of the total synthesis work on (–)-brevianamide B (**38**), an interesting result was obtained that would prove important for the paraherquamide synthesis. In an attempt to increase the ratio of the desired S_N2' product **96**, the allylic chloride **95** was treated with a large excess (10 eq) of sodium hydride in refluxing benzene. Surprisingly, the undesired diastereomer **100** was primarily obtained (97:3) and in 82% overall yield.

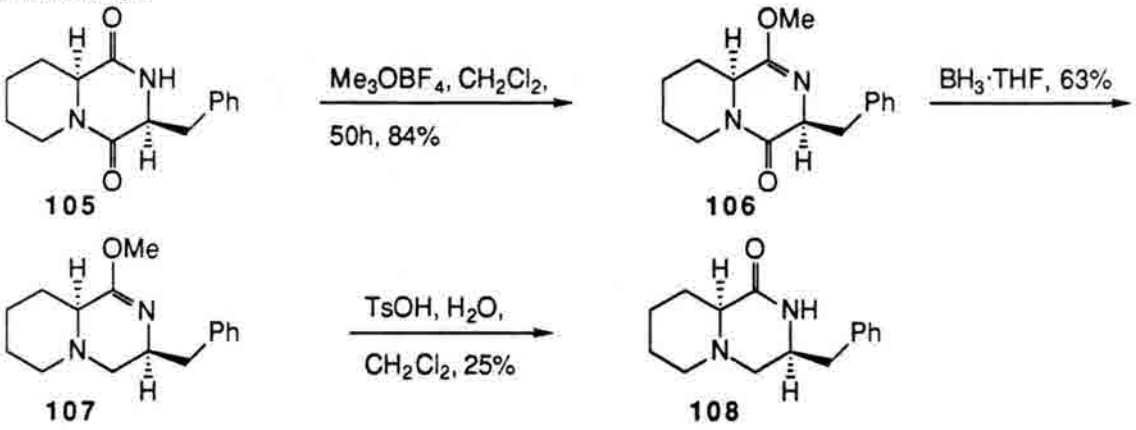
Scheme 30



With this result in hand, Williams *et al.*. undertook a simple model study [24b] to shed some light on the paraherquamide synthesis. In a reaction that mimicked the cationic cyclization of brevianamide B, the unnatural product **100** was cyclized with conc. HCl in dioxane to furnish the expected indole **101**. This material was then treated with *tert*-butylhypochlorite and triethylamine in dichloromethane supplying the chloroindolenine **102** that was immediately treated with refluxing MeOH/H_2O/AcOH (50:40:10) for one

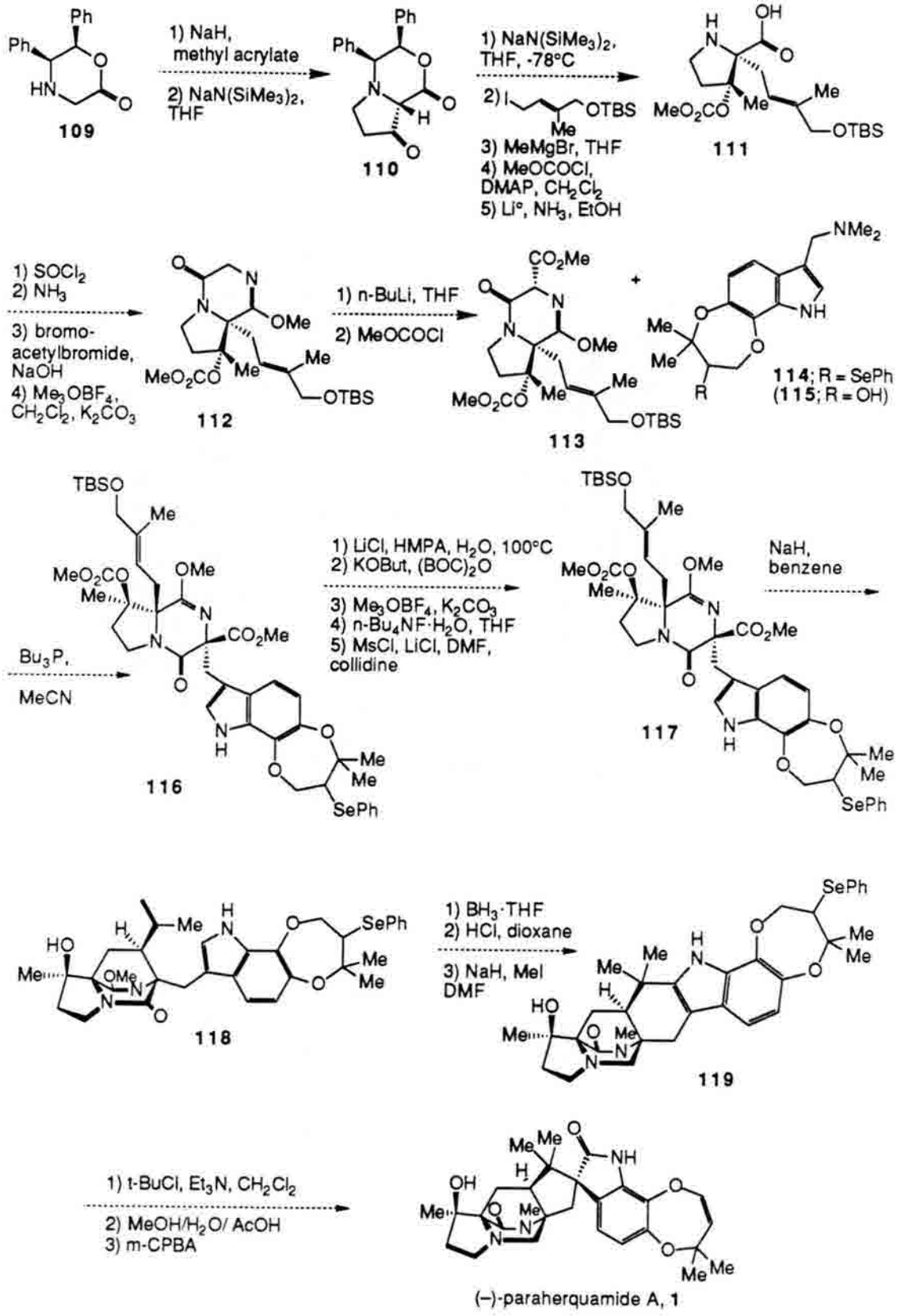
hour, leaving the desired oxindole **103** in 58% yield.[41] This product has the same relative stereochemistry as the paraherquamides. The other oxindole **104** was also obtained in 15% yield [42] (Scheme 30). This model synthesis of compound **103** explored some of the stereochemical problems for the paraherquamide synthesis, but numerous problems remained. One possible difficulty would be the conversion of the piperzinedione (as in **103**) to a monooxopiperzine like **1**. This problem of selectively reducing one amide functionality in the presence of another was explored by Williams in a short synthesis of verruculotoxin.[104] The piperzinedione **105** was obtained by the condensation of (S)-phenylalanine methyl ester hydrochloride and (R,S)-N-benzyloxycarbonyl-pipecolinic acid followed by catalytic hydrogenolysis to effect ring closure. After separation of the diastereomers, compound **105** was converted to the lactim ether **106** with trimethyloxytetrafluoroborate. This material was reduced to the desired tertiary amine **107** in 63% yield. Finally deblocking of the lactim ether was done with toluenesulfonic acid to provide the natural product **108** (Scheme 31).

Scheme 31



A proposed synthesis of paraherquamide A (**1**) employing this solution, and the other ideas is outlined in Scheme 32. The proposed method to synthesize the unique hydroxy,methyl proline derivative starts with the oxazinone **109**. This would provide the required stereochemistry at the 14- and 13-position of **1**. The alkylation of **110** would take place on the least hindered β– face of this bicyclic structure, because the α– face is effectively

Scheme 32


1) NaH, methyl acrylate
2) NaN(SiMe3)2, THF
1) NaN(SiMe3)2, THF, -78°C
2) I OTBS Me
3) MeMgBr, THF
4) MeOCOCl, DMAP, CH2Cl2
5) Li°, NH3, EtOH
1) SOCl2
2) NH3
3) bromo-acetylbromide, NaOH
4) Me3OBF4, CH2Cl2, K2CO3
1) n-BuLi, THF
2) MeOCOCl
1) LiCl, HMPA, H2O, 100°C
2) KOBut, (BOC)2O
3) Me3OBF4, K2CO3
4) n-Bu4NF·H2O, THF
5) MsCl, LiCl, DMF, collidine
NaH, benzene
Bu3P, MeCN
1) BH3·THF
2) HCl, dioxane
3) NaH, MeI DMF
1) t-BuCl, Et3N, CH2Cl2
2) MeOH/H2O/ AcOH
3) m-CPBA
109
110
111
112
113
114; R = SePh
(115; R = OH)
116
117
118
119
(–)-paraherquamide A, 1

blocked by the vicinal phenyl groups. The ketone would then be methylated and the resulting tertiary alcohol trapped as the carbonate. This sets up the required stereochemistry, placing the proline **111** in the D-configuration. After further manipulations the required methyl carboxylate **113** is ready for the Somei alkylation with the gramine **114.** Most of the remainder of this synthetic strategy has already been discussed. It is likely that the reduction as written would have to be performed after the cationic cyclization. In any event, this approach became the blueprint for all later work on the synthesis of **1** and (+)-paraherquamide B (**3**). It must be pointed out that the dioxepin gramine **114** as shown in this synthetic strategy was expected to be the target because of work completed in chapter two. Therefore, this proposed synthesis was not entirely elaborated until the work of chapter two was well under way (Scheme 32).

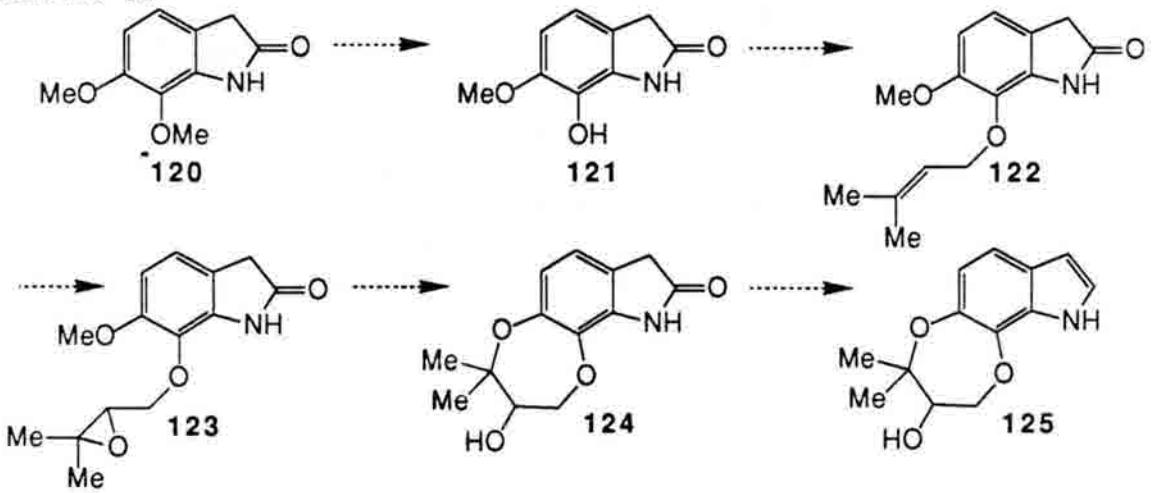
CHAPTER TWO

THE SYNTHESIS OF THE DIOXEPIN-INDOLE OF PARAHERQUAMIDES A & B

2.1 Early Studies Toward the Synthesis of the Dioxepin–Indole of the Paraherquamides

For any synthesis there is usually a number of possible approaches to the target molecule. The problem comes in choosing the most desirable and workable route. A successful multistage synthesis is versatile, contains high yielding steps, and uses a minimal amount of chromatography especially in the early stages. With these thoughts in mind, we pointed our efforts at 6,7-dimethoxyoxindole (**120**).[43] We thought that the 7-methoxy group could be preferentially demethylated, and the resulting oxindole **121** alkylated and epoxidized. The epoxide **123** could be treated with a Lewis acid (or Bronsted acid) to effect demethylation, and concomitant cyclization, providing the required oxindole **124**. This oxindole could be reduced to the indole **125** and then converted to the gramine giving the required dioxepin–indole **115** (Scheme 33)

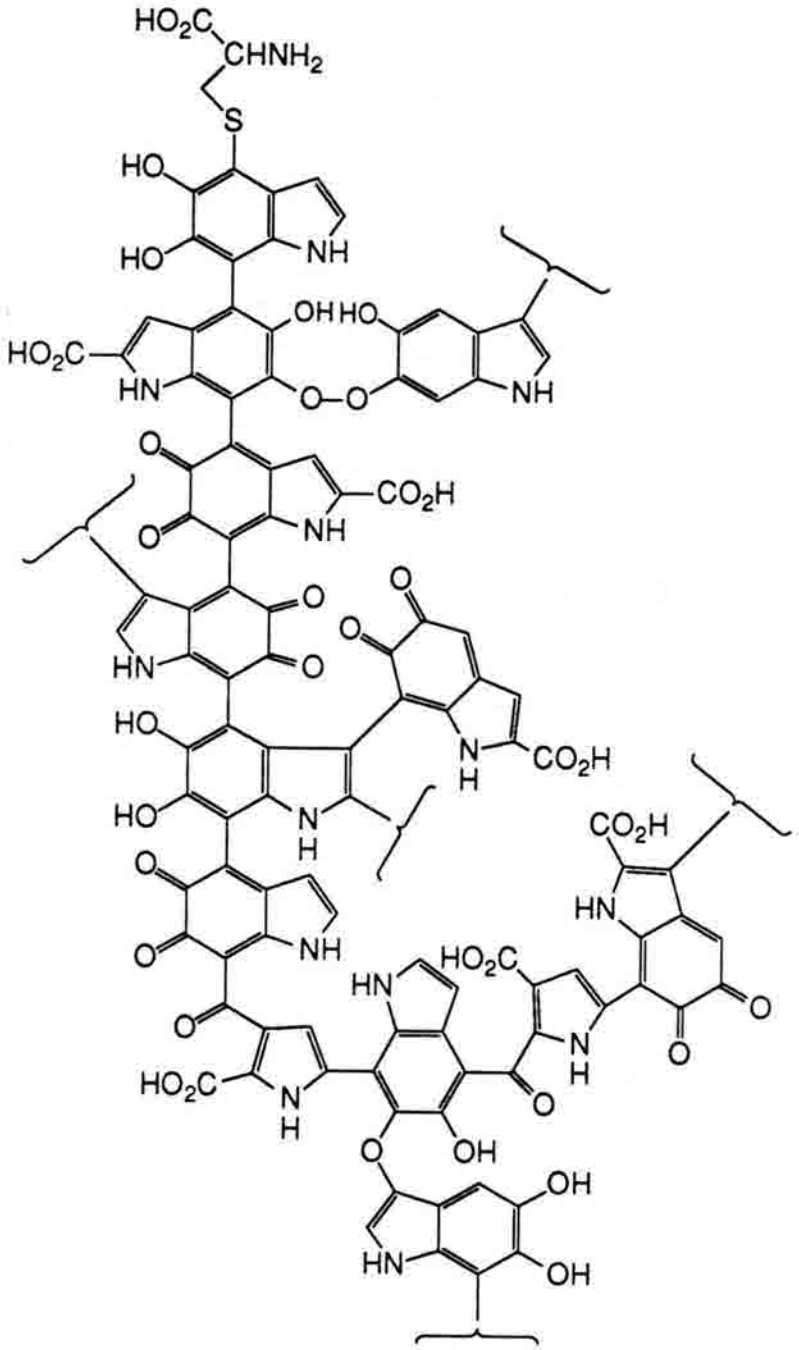
Scheme 33



This approach was attractive for a number of reasons. First, indole **120** is a known compound. Second, it is known that oxygenated indoles are notoriously unstable. They are prone to autooxidation,[44] photooxidation [45] dimerization and polymerization.[46] In fact 5,6-dihydroxyindole **126** is a precursor to the indolic polymer melanin, a human skin pigment [47] (Figure 1). The corresponding 6,7-dihydroxyindole (**128**) is also a known compound,[48a] and would probably behave in a similar manner.[49] The mechanism for the autooxidation of 5,6-dihydroxyindole **126** could also apply to **128** (Scheme 34).

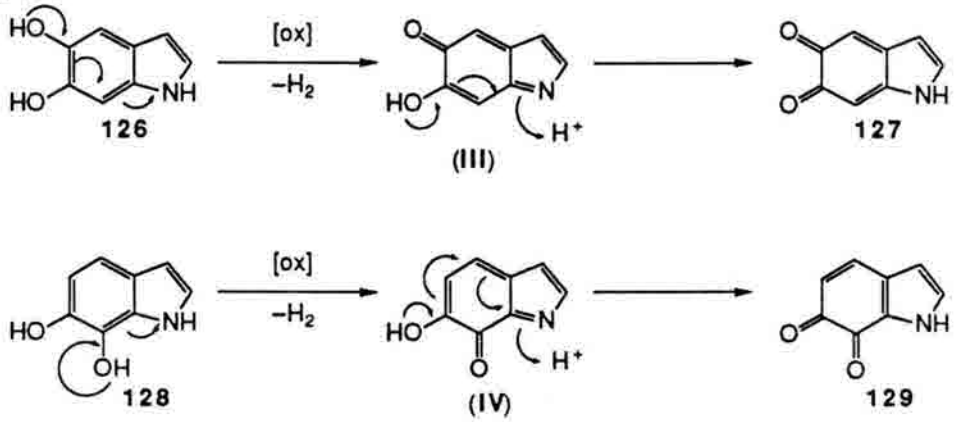
Dealing with oxygenated indoles particularly in the presence of acids or, in oxidizing environments would be difficult. It therefore seemed prudent to start with an oxindole and convert it to an indole only at the end.

Figure 1



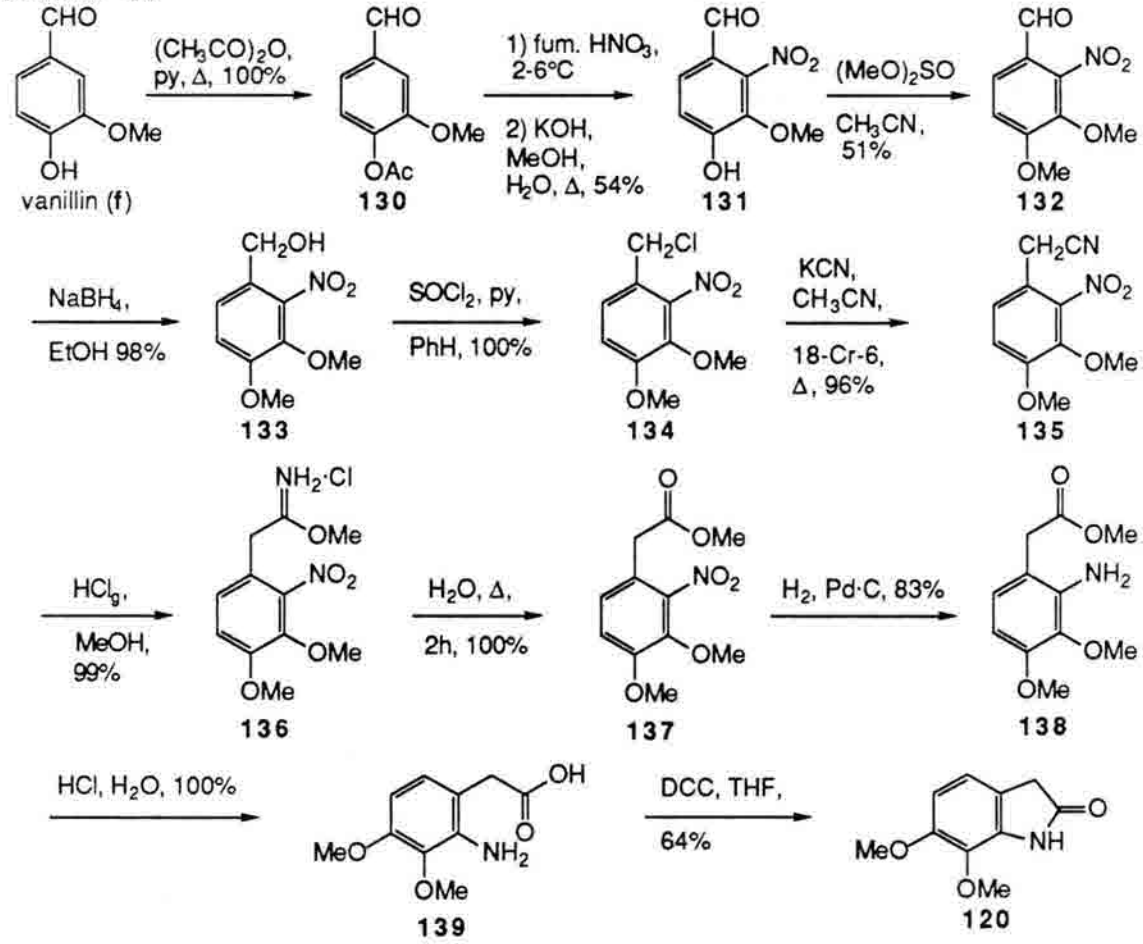
eumelanin chromophore monomer unit (**e**)

Scheme 34



We modified Robinson's synthesis of 6,7-dimethoxyoxindole (**120**), formed by the hydrolysis of an azlactone. Our new synthesis side stepped that approach (Scheme 35).

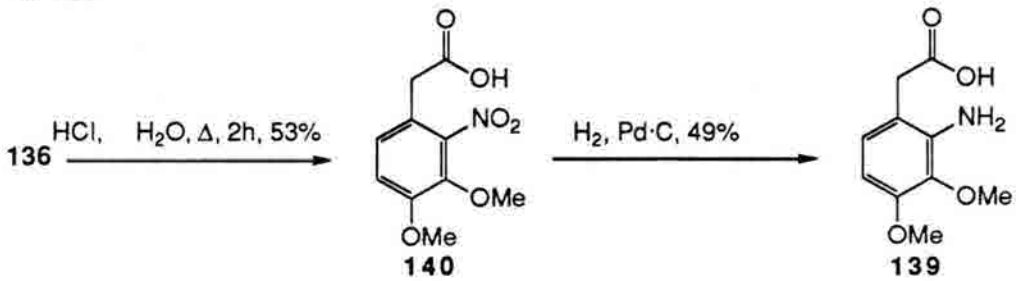
Scheme 35



Vanillin (**f**) was acetylated providing **130** in quantitative yield. This was treated with cold, fuming nitric acid followed by basic hydrolysis (refluxing KOH) to furnish 2-

nitrovanillin (**131**) in 54% yield.[48a] This was then refluxed with dimethylsulfate in acetonitrile supplying the dimethoxy compound **132**,[48a,b,50] which was subsequently reduced to supply the alcohol **133**.[51] The alcohol was then converted to the chloride **134** with thionyl chloride, followed by treatment with KCN delivering the nitrile **135**. A Pinner reaction (HCl_g, MeOH, 99%) formed the imino-ether hydrochloride **136**, which was hydrolyzed to the methyl ester **137** in quantitative yield. The nitro group of the methyl ester was then reduced [52] yielding the methyl ester **138** and hydrolyzed to the acid **139**,[43] and cyclized to the oxindole **140** with DCC in 64% yield (Scheme 35). An attempt was made to transform **136** to **139** directly, but the yields were lower (Scheme 36). While the synthesis of **120** was a fairly lengthy 12 steps, the overall yield was 12%, and it had the additional advantage that only a minimal amount of purification was necessary.

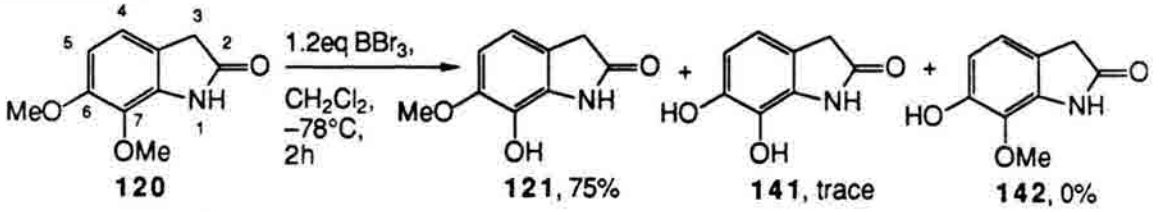
Scheme 36



With compound **120** readily accessible, we moved forward to deprotect the 7-methoxy group.[53] We thought that by using a limited amount of a Lewis acid it would attack the 7-position preferentially. The amide nitrogen and the 7-position oxygen, should form a bridging borocycle with concomitant nucleophillic attack of the methyl group by the bromide ion. This proved to be correct. When **120** was treated with boron tribromide in methylene chloride, the primary product was the desired 6-methoxy, 7-hydroxyoxindole (**121**); however, there were problems with this step. The product **121** proved difficult to separate from unreacted starting material; plus, both compounds do not dissolve readily in organic solvents. There was also some evidence that small amounts of the doubly deprotected compound **141** was formed during the reaction, and it appeared to be unstable.

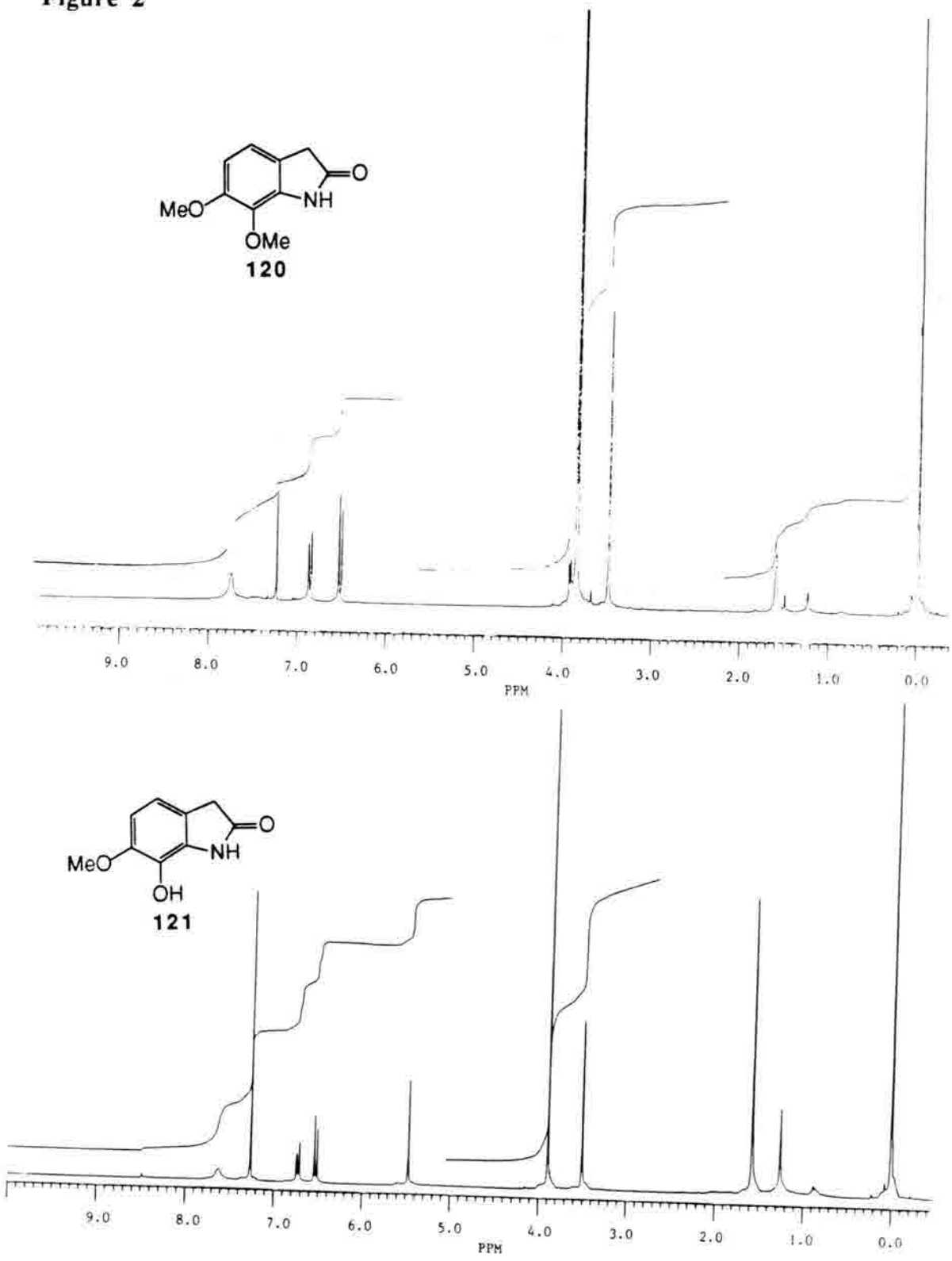
However, none of the other isomeric 6-hydroxy, 7-methoxyoxindole (**142**) was ever detected (Scheme 37)

Scheme 37



The absolute proof of structure would come later, but the working hypothesis that the major product was **121** and not the regioisomer **142** came from the proton nmr chemical shifts. The ^{1}H nmr of starting material **120** has the two ring protons as two doublets; one centered at δ 6.86 (d, J = 8.2Hz) and the other at δ 6.52 (d, J = 8.2Hz). The presumed to be **121** has one ring proton centered at δ 6.73 (d, J = 8.0Hz) and the other at δ 6.52 (d J = 8.0Hz). In both cases there is one doublet centered at 6.52 ppm. This proton is undoubtedly the C-5-H in the case of **120** because of its greater upfield shift relative to C-4-H. Both the C-5-H and C-4-H are in similar electronic environments with respect to the two methoxy groups (one ortho interaction, one para interaction and two meta interactions). The ortho, para interactions are relatively equal; however, one of the two protons is affected differently by the amide group (an ortho/para activating group,therefore having larger shielding effect on the proton). The proton that is para- to this amide should be shifted higher upfield compared to the one that is meta- to the amide. The methylene group should play only a tiny role comparatively. This argument should also hold in the case of **121** since the difference between the activating abilities of a methoxy group and a hydroxy group is smaller than the difference between the amide group and the methylene group. This must be the case since the chemical shifts of this C-5-H proton is exactly the same in both **120** and **121**. The C-4-H signal of **121** is shifted upfield (0.13ppm) relative to **120**. This signal must show either a para- or ortho- interaction in order for it to have such a large shift, and the only way to rationalize this is, if the 7-position bears a hydroxyl group (Figure 2).

Figure 2

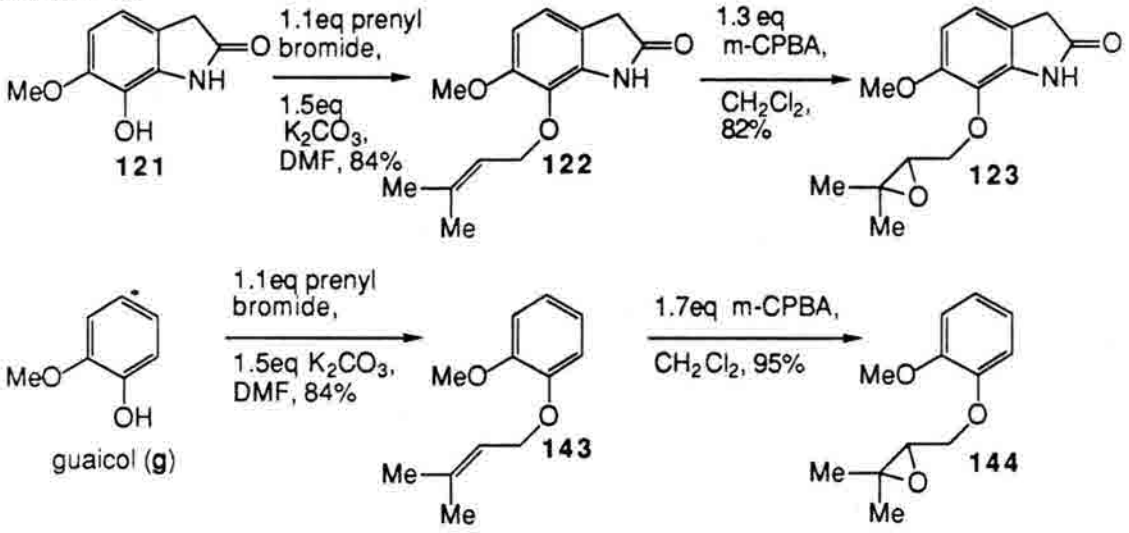


It was interesting to speculate on the appearance of the nmr spectrum of isomer **142**. Presumably the C-5-H would be shifted upfield relative to the C-4-H for similar

reasons. This later turned out to be correct. The nmr spectrum of **142** has a doublet centered at 6.86 ppm exactly like the 4-H of **120**, and a doublet corresponding to 5-H centered at 6.60 ppm. The spectrum of **141** was similar, but both doublets were shifted upfield to 6.36 and 6.48 ppm. (The synthesis of **141** and **142** will be described below).

The oxindole **121** was alkylated with prenyl bromide giving the desired compound **122**, which was easily epoxidized (1.3 eq m-CPBA, CH_2Cl_2, 0 °C, 2.5h, 82%) providing the required precursor **123.** At this juncture it was deemed prudent to carry out a simple model study. Guaicol (**g**) was alkylated in the same manner as before with prenyl bromide in dimethylformamide producing **143**, which was epoxidized as before to afford the required model epoxide **144** in 95% yield (Scheme38).

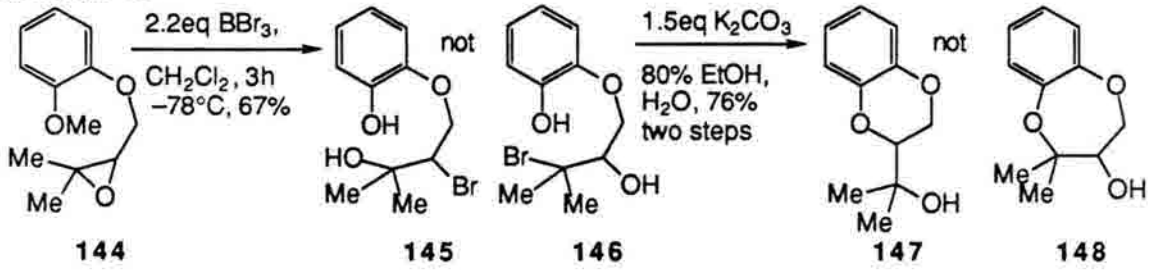
Scheme 38



The problem now, was to simultaneously deprotect the methoxy group and then cyclize the epoxide [54] Compound **144** was treated with boron tribromide and monitored by TLC. After the disappearance of starting material the crude reaction mixture was poured into water and extracted with methylene chloride. The crude oil was isolated, and chromatagraphed, producing a light brown oil. The rest of the material was found to decompose in time. This oil was initially assigned the structure **146** (67% from **144**), but there was no trace of the expected dioxepin **148**. This phenol (actually **145**) was treated under conditions conducive for S_N1 reactions (80% EtOH, H_2O). However, the product

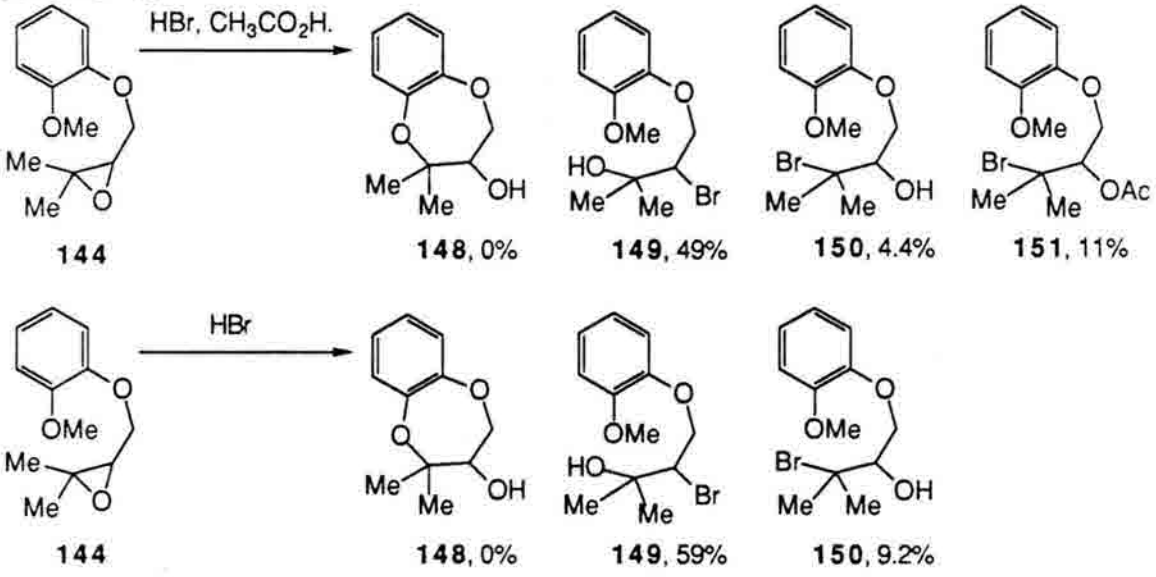
isolated proved to be the tertiary alcohol **147**, when it failed the Jones oxidation test [55] (Scheme 39).

Scheme 39



A few other experiments along these lines were also tried. It is known that concentrated HBr in acetic acid demethylates anisoles,[56] and this particular combination is also a very strong ionizing solvent. We expected that the epoxide would solvolyze providing the more stabilized tertiary carbocation, and then close on the phenol. This reaction did not work as predicted. No cyclized product was found and only a small amount of the compounds with the expected orientation were formed. Epoxide **144** was also treated with HBr in trifluoroacetic acid, and trimethylsilyl iodide in $CHCl_3$,[57] with similar results (Scheme 40).

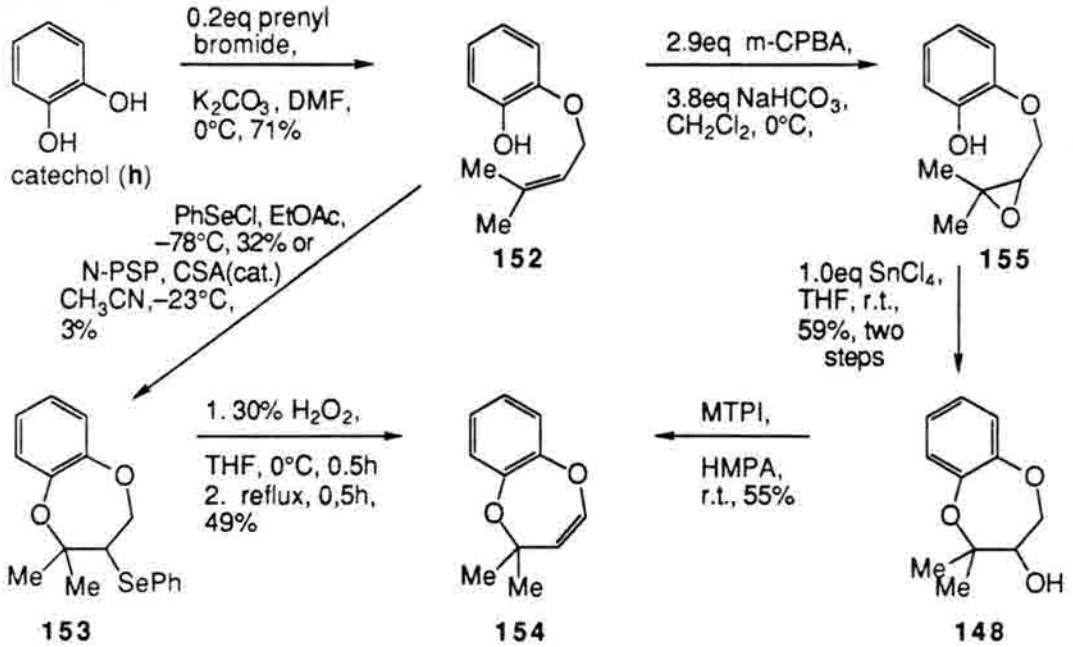
Scheme 40



This same type of reaction was attempted on the oxindole **123**, but no desired products were formed. Attempts were also made to demethylate compound **143**. Anisole

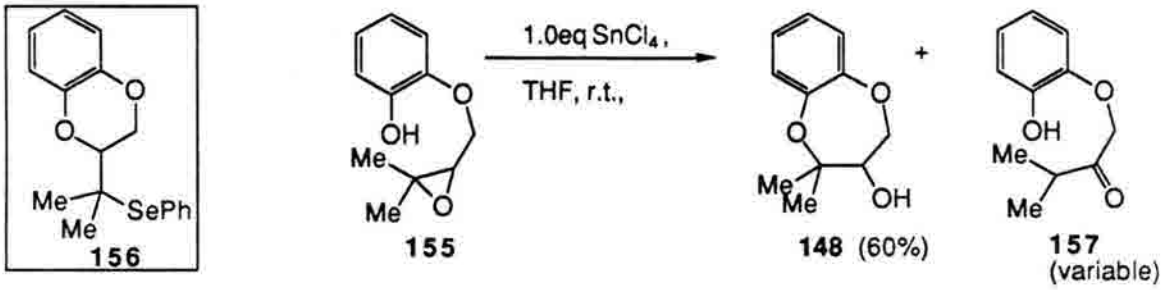
143 was treated with 1.2eq of BBr_3 (or BCl_3) at –78 °C in CH_2Cl_2 for one hour, but only a small amount of the desired product **152** was obtained (4%). These results were disappointing. There seemed little chance for this approach to give the desired product. This synthetic strategy was reluctantly set aside for the time being. Later, compounds **121** and particularly **141** would prove invaluable. In any event, the entire cyclization reaction was re-explored. We thought that it would be much easier to accomplish the reaction by starting from the unmethylated prenylated material (Scheme 41). Catechol (**h**) was mono-O-alkylated in good yield (71%), by using an excess of the substrate. We envisioned **152** cyclizing with an electrophilic source of selenium, since these type of ring forming reactions are known.[58] Following a procedure of Clive,[59] **152** cyclized to **153** although in very low yield. The main byproducts came from the addition of the PhSeCl across the double bond, electrophilic aromatic substitution of the phenyl ring by the phenylselenide, and phenolic attack at the methylene producing the 6-membered ring product **156**. In an attempt to obviate these deleterious side effects, the prenylated catechol **151** was treated with N-phenylselenophthalimide (N-PSP).

Scheme 41



N-PSP is reported [60] to give less addition across the double bond because the counter ion (phthalimide) is less reactive than chloride; however in our case the yield was considerably lower. In any event **153** was treated with H_2O_2 to oxidize the selenide. The resulting selenoxide was thermally eliminated by refluxing the solution, providing the unique dioxepin **154** in 49% yield. The use of an epoxide was also reexamined, and a thorough search of the literature turned up an interesting study by Cookson *et al.*.[61] During the course of the a total synthesis of zoapatanol [62] (a seven-membered ring oxepane) the intramolecular cyclization of epoxy alcohols using several acids was compared. The best selectivity for seven-membered ring vs 6-membered ring formation was 20:1 with stannic chloride ($SnCl_4$). In contrast, $BF_3{\cdot}Et_2O$ gave only a 2:1 ratio under optimum conditions. A subsequent synthesis of this molecule by Kocienski using the same procedure [63] was reported, so this reaction strategy was applied to the case at hand. The prenylated catechol **152** was treated with m-CPBA, but problems were encountered. The epoxide was somewhat unstable under the reaction conditions. Sodium bicarbonate was added to the reaction mixture neutralizing the m-chlorobenzoic acid. These conditions prevented an acid-catalyzed cyclization that led to the undesired 6-membered ring alcohol **147**. The epoxide **152**, also has a tendency to cyclize when in contact with silica gel giving **147** as well as a small amount of the desired product **148**. It was found that the most efficient way of dealing with this problem was to add the $NaHCO_3$ and m-CPBA sequentially (approx.1.0eq every few hours for 5.5 hours). The epoxide **155** was then taken on to the next step without performing any chromatography. This cyclization step was no less troubling. Treatment of **155** with stannic chloride a 1,2 hydride shift was observed, providing the useless ketone **157** as the major side product. This reaction is not unprecedented. A synthetic investigation of Friedel–Crafts cyclialkylations of various epoxides with tin tetrachloride, it was found that this same type of hydride shift was the main side reaction [64] (Scheme 42).

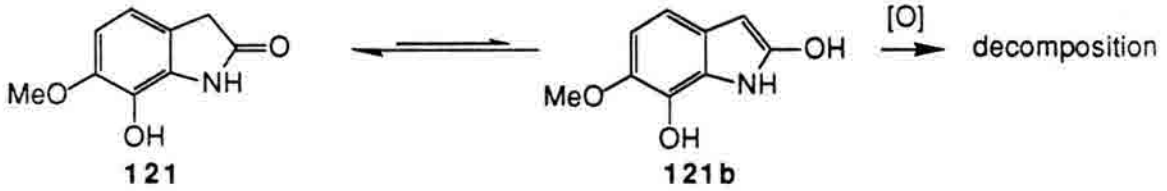
Scheme 42



A number of methods were explored to effect the elimination of the secondary alcohol of **148**. Conversion of **148** to the mesylate (MsCl, Et_3N, THF) followed by basic elimination(DBU) gave the desired dioxepin **154** in low (36%) yield. When **148** was subjected to *o*-nitrophenyl selenocyanate and t-butyl phosphine,[65] the TLC showed a multitude of products. Finally the alcohol was smoothly eliminated with methyltriphenoxyphosphonium iodide (MTPI) in HMPA to provide **154** (55% recrystallized).[66]

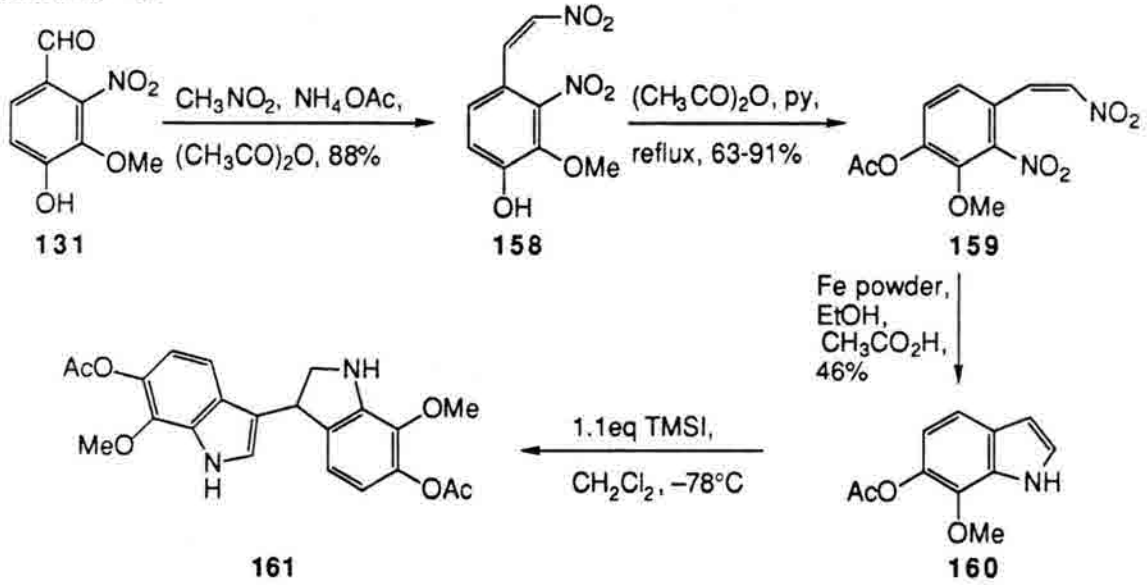
There were now two methods to perform the key 7-membered ring cyclization, and two distinct procedures to form the hitherto unknown dioxepin ring system.[67] The remaining problem, was how to get the rest of the desired ring structure. The main problem was to distinguish between the two hydroxy functional groups of a suitable precursor like, 6,7-dihydroxyoxindole (**141**). As mentioned earlier, there was some evidence that compounds like this are unstable. During thin layer chromatography, the band corresponding to **141** turned a very dark color. This was not too surprising considering how oxindoles have some indole characteristics due to tautomerization (Scheme 43). The failure to separate the oxindoles **120** and **121** by a basic extraction (1M NaOH) demonstrated this fact.

Scheme 43



The obvious solution was to pick a different protecting group for the 6-position of the oxindole. The idea was to repeat the synthesis of 6,7-dimethoxyoxindole (**120**), but without the 4-methoxy group of **132.** Unfortunately, attempts at reducing the aldehyde of **130** proved futile. The likely problem was the unprotected hydroxy group para- to the aldehyde. An attempt was made at reducing the 4-acetoxy derivative, but with similar results. At this time a short synthesis of the known 6-acetoxy-7-methoxyindole (**160**) [68] was undertaken. Perhaps the indole might not be as unstable as originally thought. This was easily accomplished in three steps from *o*-nitrovanillin (**131**). However, difficulties with the demethylation step reconfirmed our suspicions. Treatment of **160** with a fairly mild Lewis acid(1.1eq TMSI, CH_2Cl_2) [69] produced the dimer **161**. The indole **160** was also unstable in solution (Scheme 44).

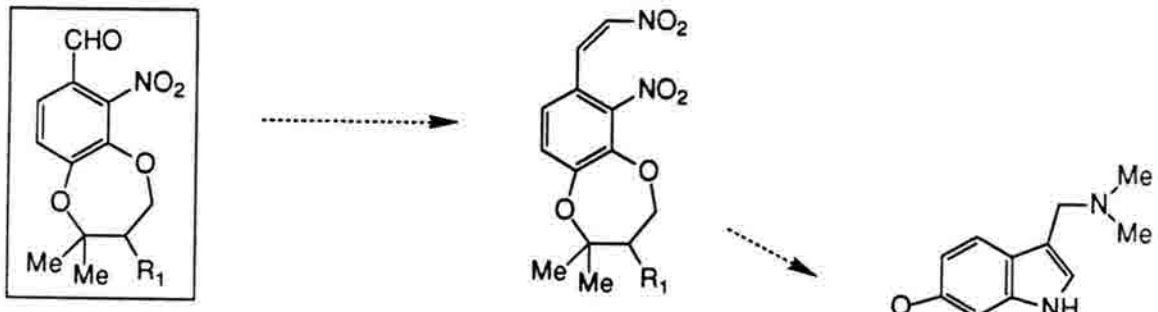
Scheme 44



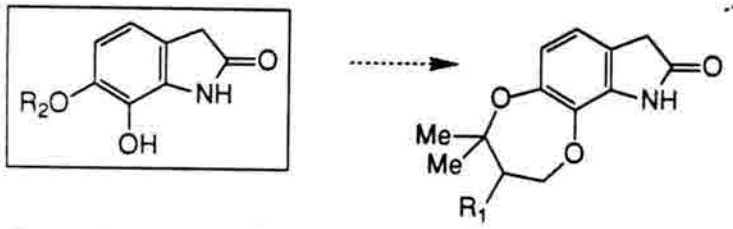
This latest difficulty led us to rethink our strategy. We decided on a two-pronged attack. The first approach would mimic the α–,β–dinitrostryene method in Scheme 44, but with the dioxepin formed prior to indole formation. In this way we thought to minimize any instability inherent in oxygenated indoles. The second approach would rely on the more stable oxindole and convert it to an indole only at the end (Scheme 45).

Scheme 45

APPROACH 1



APPROACH 2



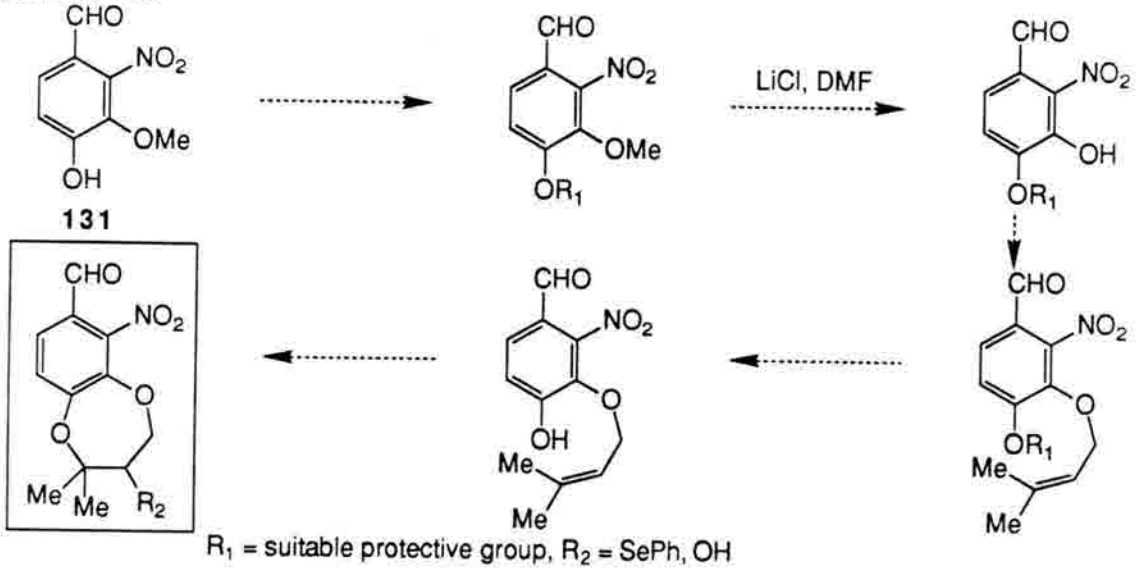
114; R_1 = SePh
115; R_1 = OH

R_2 = suitable protective group

2.2 The Synthesis of Various Dioxepins, Approach 1

The centerpiece of this approach involves the mild deprotection (LiCl, DMF) of the 3-methoxy group of *o*-nitroanisoles.[70] The generalized plan for this approach is outlined below (Scheme 46).

Scheme 46

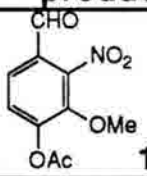
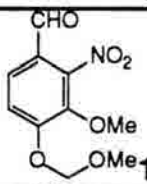
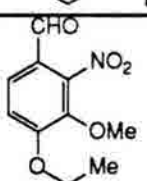
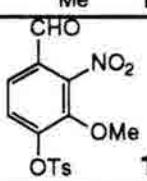
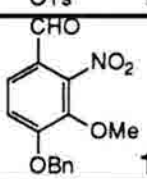


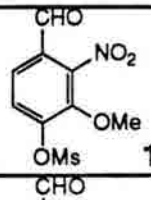
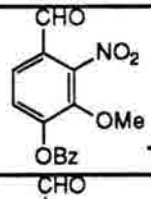
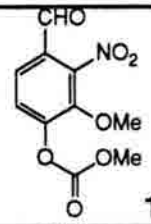
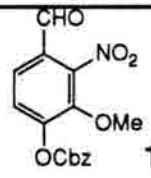
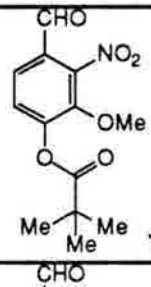
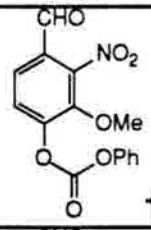
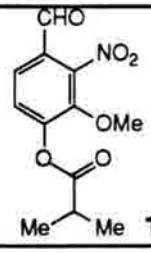
R_1 = suitable protective group, R_2 = SePh, OH

Numerous vanillin analogs were made quickly and easily in preparation for the demethylation step. A number of the protective groups were chosen because of their acid lability, but the most effective groups were acid stable and base labile. The final group, the sulfonate esters are known to be resistant to both acid and base. This is summarized below (Table 3).

Table 3

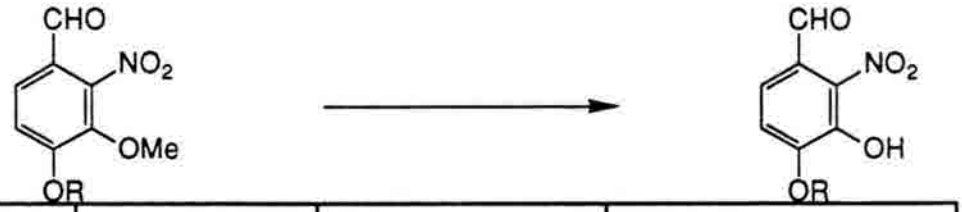
131

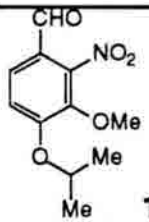
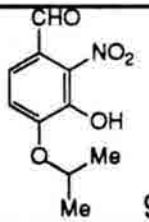
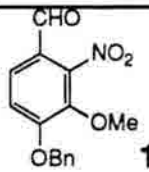
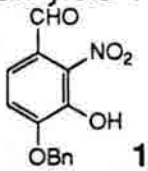
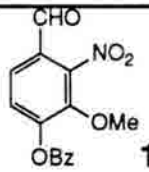
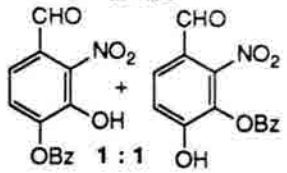
entry	R	conditions	yield	product
1	Ac	$(Ac)_2O$	see **131**	 **162**
2	$-CH_2OCH_3$	MOMCl NaH, THF	93%	 **163**
3[71]	$-CH(CH_3)_2$	isopropyl-bromide K_2CO_3, DMF	98%	 **164**
4	Tosyl (Ts)	TsCl, K_2CO_3, acetone	100%	 **165**
5	Benzyl (Bn)	BnBr, K_2CO_3, DMF	100%	 **166**

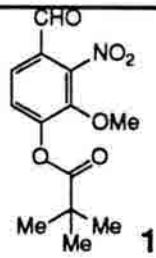
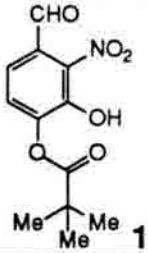
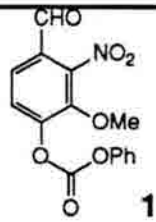
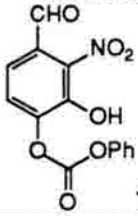
6	Mesyl (Ms)	MsCl, pyridine	53%	 **167**
7	Bz	benzoyl-chloride, py, dioxane	100%	 **168**
8	-C(O)OCH$_3$	methyl-chloroformate K_2CO_3, DMF	50%	 **169**
9	Cbz	benzoyl-chloro-formate py, THF	71%	 **170**
10	pv	pivaloyl-chloride, pyridine	66%	 **171**
11	-CO$_2$Ph	Phenyl-chloroformate pyridine,THF	34%	 **172**
12	-COCH(Me)$_2$	isobutyric anhydride pyridine,THF	66%	 **173**

The key demethylation step was next. The only really encouraging result was with the benzoyl protected vanillin **168**; the benzyl material **166**; and the isopropyl protected nitro-vanillin **131** (Table 4).

Table 4

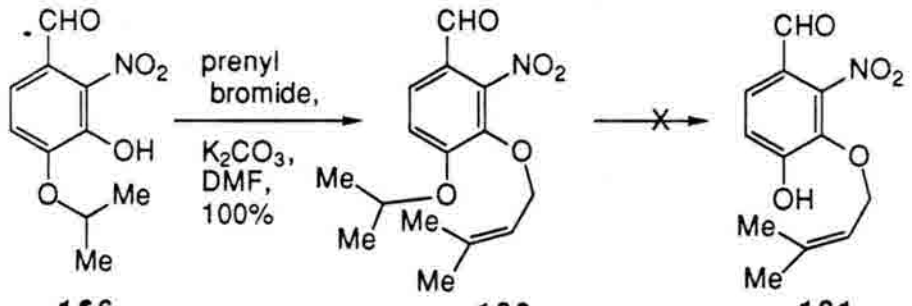


entry	compound	conditions	yield/product(s)
1	**162**	2.0eq LiCl, 0.5M DMF, 4.5 hours	no recognizable product
2	**163**	1.1eq LiCl, O.3M DMF, 130 °C, 1h	40% nitrovanillin, **131**
3	 **164**	4.0eq LiCl, 0.5M DMF, 100–130 °C 24h	 91%,**174**
4	**165**	3.0eq LiCl, DMF, 115 °C, 45min	13%,nitrovanillin, **131**
5	 **166**	1.1eq LiCl, 0.5M DMF, 100 °C, 2.5h then 3.0eq LICl, 24h, r.t.	low yield + **131**  **175**
6	**167**	3.0eq LiCl, 0 5M DMF, 70 °C, 1.5h	48% nitrovanillin, **131**
7	 **168**	3.0eq LiCl, 0.5M DMF, 85 °C, 2h	24%  **176** **177**
8	**169**	no reaction attempted	
9	**170**	3.0eq LiCl, 0.5M DMF, 50–75 °C, 4h	quant. nitrovanillin, **131**

10	 **171**	3.0eq LiCl, 0.45M DMF, 80 °C, 3h	**77** +trace  **178**
11	 **172**	3.0eq LiCl, 0.13M DMF, 75 °C, 4h, r.t. 15h	trace of  **179**

These experiments had one thing in common: most of the products, particularly the ester and carbonate products were unstable. The most stable material was the isopropyl product **174**. This substance was prenylated to give the alkylated nitro-compound **180** in quantitative yield. Numerous methods were tried to remove the isopropyl group, but it was found that the prenyl group came off more readily (Table 5).

Table 5

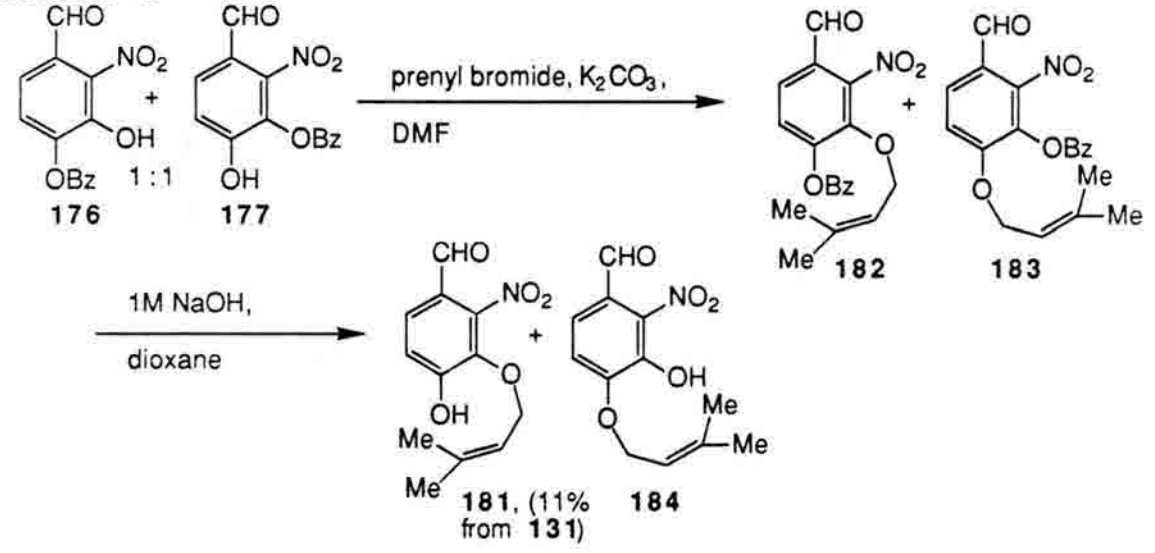


166 **180** **181**

entry	conditions, (180) to (181)	yield/products
1	1.1eq $TiCl_4$, –78 °C, 5 min.	100% **174**
2	CF_3SO_3H(cat.) CF_3CH_2OH, r.t., 1 sec.	100% **174**
3	1.1eq TMSI, CH_2Cl_2, –78 °C, 0.5h	**174** + **180**
4	18eq TFA, CH_2Cl_2, 0 °C, 1.5h	**174** + **180**
5	HF, 0 °C, 3h.	100% **180**
6	HBr, CH_3CO_2H, 50 min., r.t.	100% **180**
7	1.1eq BCl_3, CH_2Cl_2, –78 °C, 5 min.	100% **174**

The benzyl protected material **175** was treated with 2M HCl but only a trace of the desired product was obtained. The best result came from the benzoyl protected nitrovanillin (**168**), but not without problems. The benzoyl group of **176** had a tendency to migrate to the other phenol, resulting in a 1:1 mixture of regiomers. These two products (**176** and **177**) proved difficult to separate so they were used as is for the next step. The prenylation gave a mixture of the undesired and desired products **182** and **183** respectively, which were not much more amenable to chromatography. There was still some decomposition on silica gel. The benzoyl groups were easily removed with base to provide the desired and undesired isomeric phenols **181** and **184** respectively, which were separable (Scheme 47).

Scheme 47

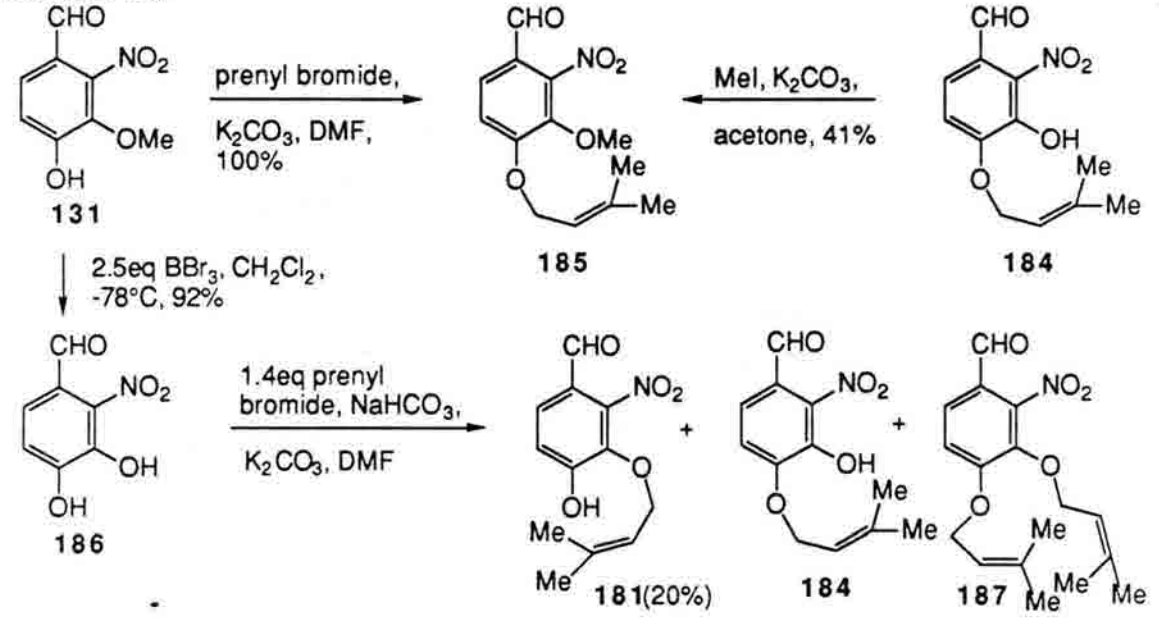


The structure of these compounds needed to be assigned. Our working hypothesis was that the less polar phenol was **184** because of the likely hydrogen bond between the phenol and the nitro-group. The desired phenol **181** could not form such a bond so it was likely to be more polar. The proof came when we prenylated nitro-vanillin (**131**), and compared that product with the product of the reaction of the undesired material (**184**) and methyl iodide. These two products **185** were identical in all respects.

This roundabout method of generating the prenylated nitro-vanillin **181**(Scheme 47) was bypassed altogether when nitro-vanillin **131** was treated with clean boron

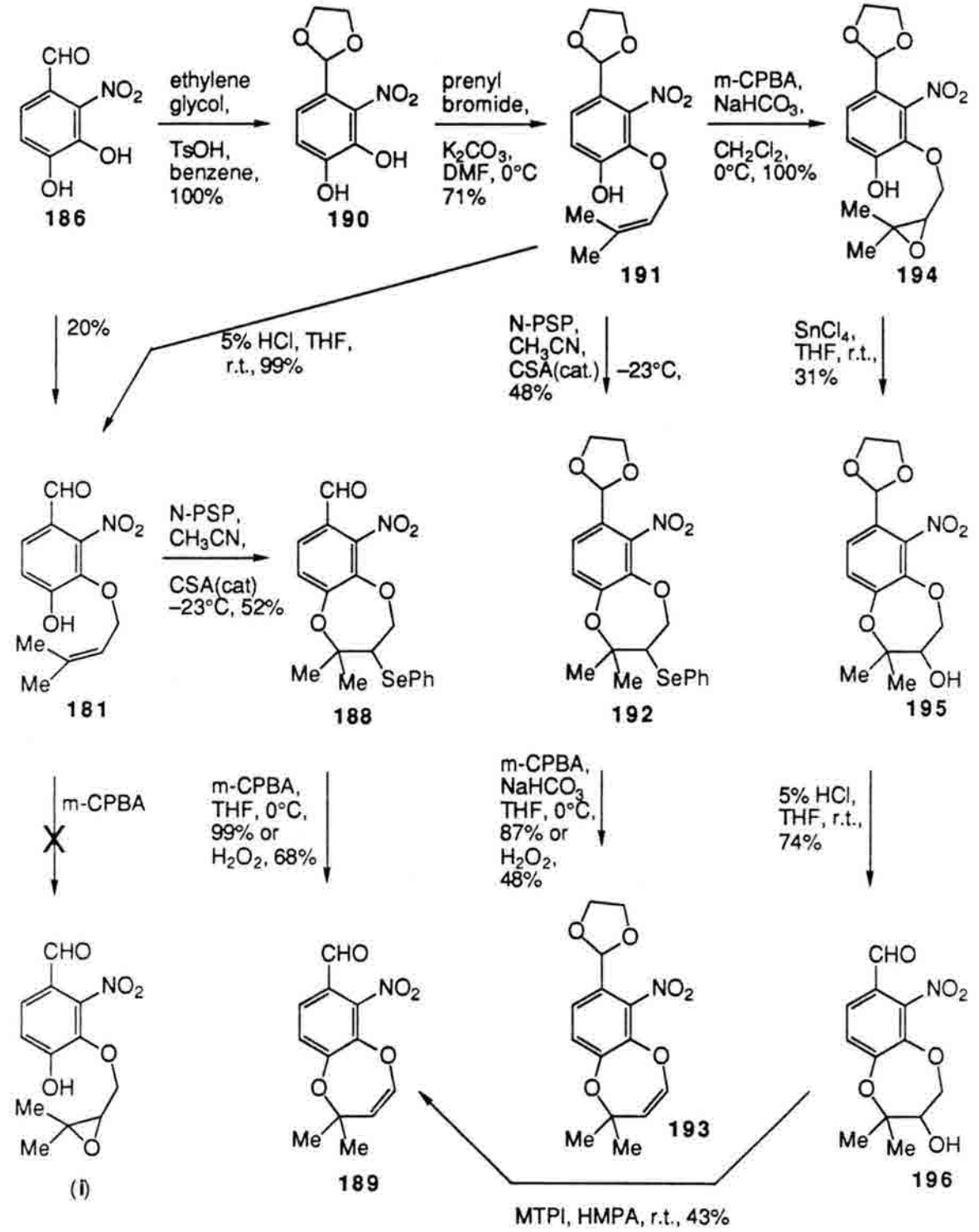
tribromide to deliver the demethylated material **186** in 92% yield. Catechol **186** was prenylated, creating three alkylated products; the desired material **181**, the undesired isomer **184**, and the bis-alkylated product **187**. This procedure proved more efficient than the route involving protecting groups; it saved two steps, and was slightly more efficient, but it was still not synthetically useful (Scheme 48).

Scheme 48



We now had a quantity of **181**, so the phenylselenoetherification reaction was attempted. Treatment of **181** with N-PSP (CH_3CN, CSA(cat.)–23 °C) resulted in the formation of the seven-membered ring selenide **188** in 52% yield. The main byproduct in this reaction was the corresponding six-membered ring selenide **214**. The ease of this reaction relative to the model system is no doubt due to the electron withdrawing ability of the other substiuents, thereby limiting the aromatic substitution byproducts. The dioxepin **189** was produced by eliminating the selenide from **188**. This was done in two ways, either with 30% H_2O_2 or with m-CPBA. These results were encouraging, but we still had to get around the problematic prenylation step. We thought that by converting the electron withdrawing aldehyde of **186** to an electron donating acetal, the pK_a or nucleophilic difference between the two hydroxy groups would change.

Scheme 49



It was envisioned that the 4-hydroxy group should become less acidic, since the aldehyde group is no longer deactivating the ring. This would effectively increase the relative acidity of the 3-hydroxy group. After **186** was converted to the acetal **190**, the

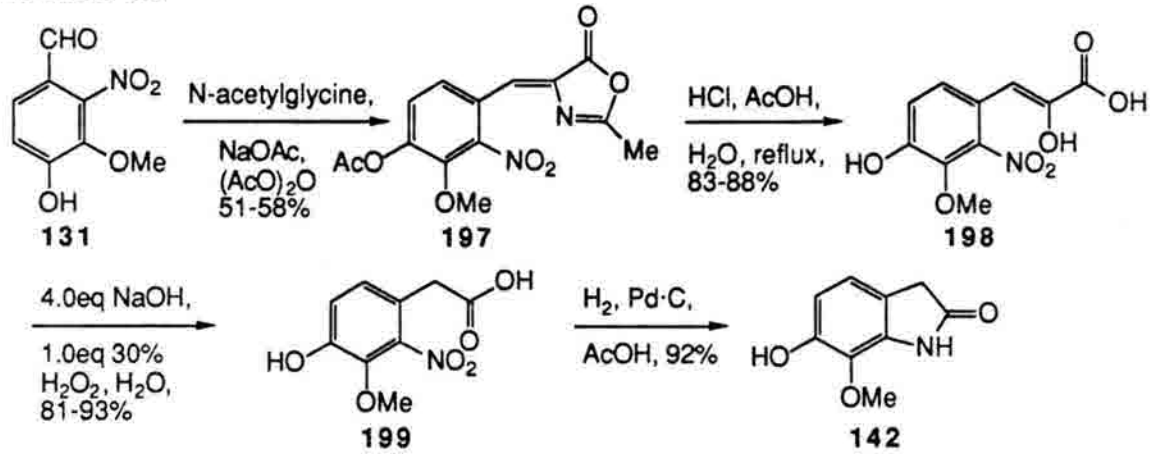
yield of the prenylated compound **191** improved significantly (71%). This material (**190**) was then efficiently deblocked (5% HCl, THF, r.t. 99%) providing **181** or cyclized with N-PSP affording the selenide **192** in 48% yield. The acetal protected selenide was then oxidatively eliminated (m-CPBA, $NaHCO_3$, THF, 0 °C, 87%) to furnish **193**. The other method of cyclization gave us conflicting results. While the acetal protected compound **191** was easily epoxidized with a buffered mixture of m-CPBA awarding **194** in quantitative yield, the unblocked material **181** proved intractable toward epoxidation. The main product was the six-membered ring tertiary alcohol **215**, and there was also some evidence that the aldehyde functionality was being oxidized to the benzoic acid. The epoxide **194** was then cyclized to the dioxepin **195** with $SnCl_4$, but in only 31% yield. The main byproduct was the ketone **216** (14%), by way of a 1,2-hydride shift. The dioxepin **195** was deprotected (5% HCl, THF) providing **196**, which was subjected to MTPI effecting the elimination of the alcohol to provide **189** in 43% yield (Scheme 49).

These were very encouraging results but they were ultimately abandoned in favor of the alternate method (approach 2) that proved superior, and finally provided the desired compound.

2.3 The Synthesis of the Dioxepin–Indole, Approach 2

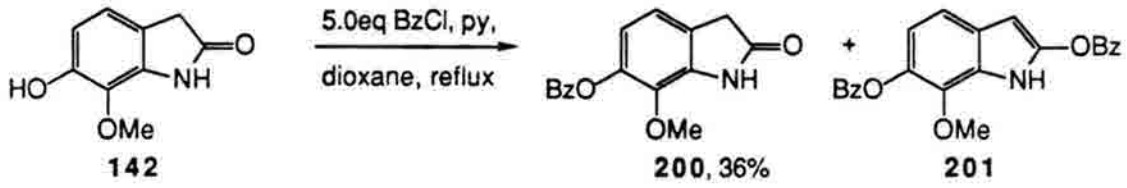
The first target of this approach was the unknown 6-hydroxy, 7-methoxyoxindole (**142**). This seemed obvious, since in the previous oxindole synthesis the deprotection of the 6-position proved impossible in the presence of a prenyloxy or epoxide functionality. By synthesizing **142** we would avoid the problem altogether. It would only be necessary to find a protective group that would allow us to differentiate between the 6- and 7-positions. We had failed to get even close to **142** by means of our previous oxindole synthesis, so we explored a different method. In 1951, Beer *et al.*, [68a] had prepared 6-hydroxy,7-methoxyindole in four steps from *o*-nitrovanillin (**131**). By modifing this procedure we were able to obtain the corresponding oxindole **142** (Scheme 50).

Scheme 50



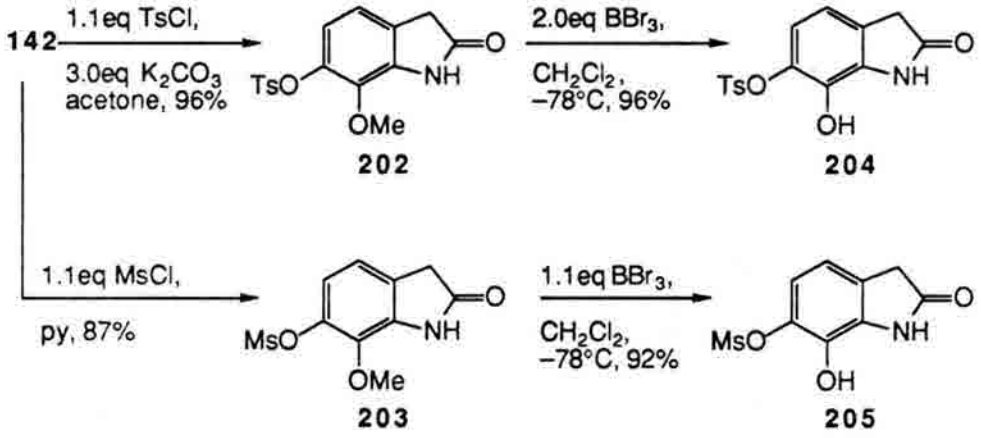
Following Beer *et al.*, **131** was condensed with N-acetylglycine to provide the corresponding azlactone. Azlactone **197** was subsequently hydrolyzed in a modification of the known procedure [68a] to provide the pyruvic acid **198**. Compound **198** was then oxidatively decarboxylated [72] to afford the phenylacetic acid **199**. Nitro compound **199** was reductively cyclized 73[34] to give the required oxindole **142** in nearly quantitative yield. This material has interesting chemical and physical characteristics. After the hydrogenolysis, if it isn't immediately removed from the solvent (AcOH), the initially white compound tends to turn black. This product would also change from a white color to a metallic gray simply by drying on the vacuum pump. These decomposition characteristics are no doubt due to its indole tautomer form. At this point we needed to select a suitable protective group. The benzoyl group was one of the few groups that could withstand the strong Lewis acid conditions for the demethylation, and the basic conditions required for the prenylation. Oxindole **142** was treated with refluxing benzoyl chloride, pyridine and dioxane supplying the required protected oxindole **200**, but in a disappointing 36% yield. The major side product was the bis-acylated compound **137** (Scheme 51). The protected oxindole **200** was subjected to TMSI in order to demethoxylate, but no identifiable products were isolated. The only other likely candidates as protective groups were the sulfonate esters.

Scheme 51



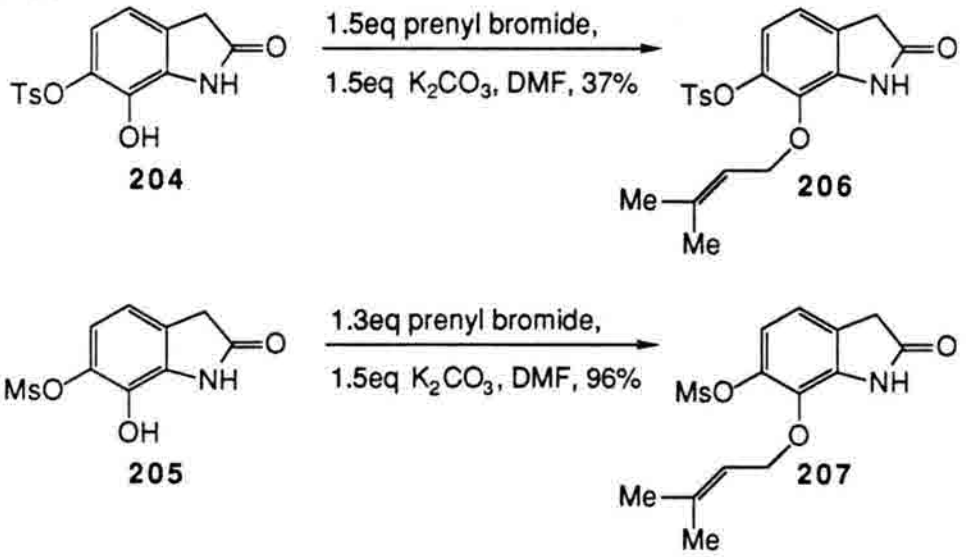
Oxindole **142** was treated with toluenesulfonyl chloride [74] and methanesulfonyl chloride,[75] giving the tosylated **202** and mesylated **203** oxindoles, respectively. They were both demethylated relatively easily giving **204** and **205** (Scheme 52)

Scheme 52



These two compounds were prenylated furnishing **206** and **207** (Scheme 53). Surprisingly, the tosylated oxindole **204** gave a poor yield of the prenylated product **206**,

Scheme 53



while the mesylate protected material granted us a high yield of **207**. The reason is probably due to the greater steric demand placed upon the tosylated oxindole **204.** The two prenylated oxindoles **206** and **207** were exposed to numerous deprotection methods. The mesylate **207** was subjected to the procedure of Woolfrom *et al.*.[74] in an attempt to hydrolyze the mesylate. However, no desired product was ever recovered. It appeared that the lactam was hydrolyzed in the process. The photolysis conditions reported by Binkley [76] were used on **206**, but the only positive result was with **202.** A TLC showed the possible formation of trace quantities of **142** (Table 6).

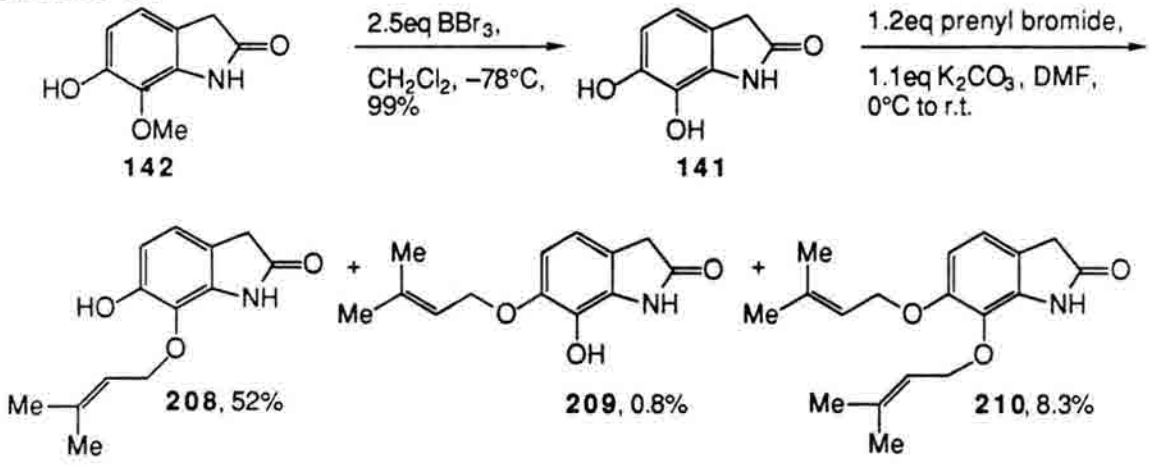
Table 6

entry	compound	base	conditions	product(s)
1	**207**	2M NaOH	–	decomposition
2	**207**	1M NaOH	30-35min, 50 °C	unidentifiable product
3	**206**	DABCO, TMSCl	hv	decomposition
4	**202**	DABCO	hv	decomposition
5	**206**	Et_3N	r.t.	no reaction
6	**202**	Et_3N	hv, 20min.	no reaction
7	**202**	Et_3N	hv, 4h	decomposition
8	**202**	K_2CO_3	reflux 1h	no reaction
9	**202**	K_2CO_3	reflux, 2h	trace **142**
10	**202**	$NaHCO_3$	reflux, 5h	trace **142**
11	**206**	K_2CO_3	85 °C, 1h	no reaction
12	**206**	K_2CO_3	85 °C, 19h	decomposition
13	**202**	H_2NNH_2	r.t., 21h	no reaction

Hydrazine was used in an attempt to nucleophilically remove the sulfonate, but that failed as well. In almost a total act of desperation, we decided to cut our losses and attempt the prenylation on the 6,7-hydroxyoxindole (**141**). This reaction was expected to behave similarly to the prenylation reaction involving the catechol **186**; thus, we expected perhaps a 20% yield of the desired oxindole **208**. Oxindole **142** was cleanly demethylated on treatment with (clear) boron tribromide. Interestingly, **142** is only slightly soluble in this

solvent, but this was not a problem since the yield of **141** is nearly quantitative. The resulting oxindole **141** material is unstable in solution turning red then brown in a short period of time. In fact, obtaining a crystal for analysis was difficult; the compound has to be recrystallized rapidly (5 min) or the crystals turn a dark red. The pure compound itself is white, and is quite stable in this form. Now that **141** had been prepared, the prenylation step was next. Much to our surprise and delight this reaction turned out to be a good one. In the presence of prenyl bromide and potassium carbonate in dimethylformamide (0 °C to r.t.) the desired alkylated product **208** was obtained in 52% yield. This result was even more startling since the undesired isomer **209** was obtained in less than 1% yield , and the bis-alkylated material **146** was produced in only 8.3% yield. Apparently, there is a great difference between the acidities of the two hydroxy groups. This is no doubt due to the influence of the activating amide functionality, donating electron density ortho- to the nitrogen, thereby increasing the relative pK_a of the 7-hydroxy group (Scheme 54).

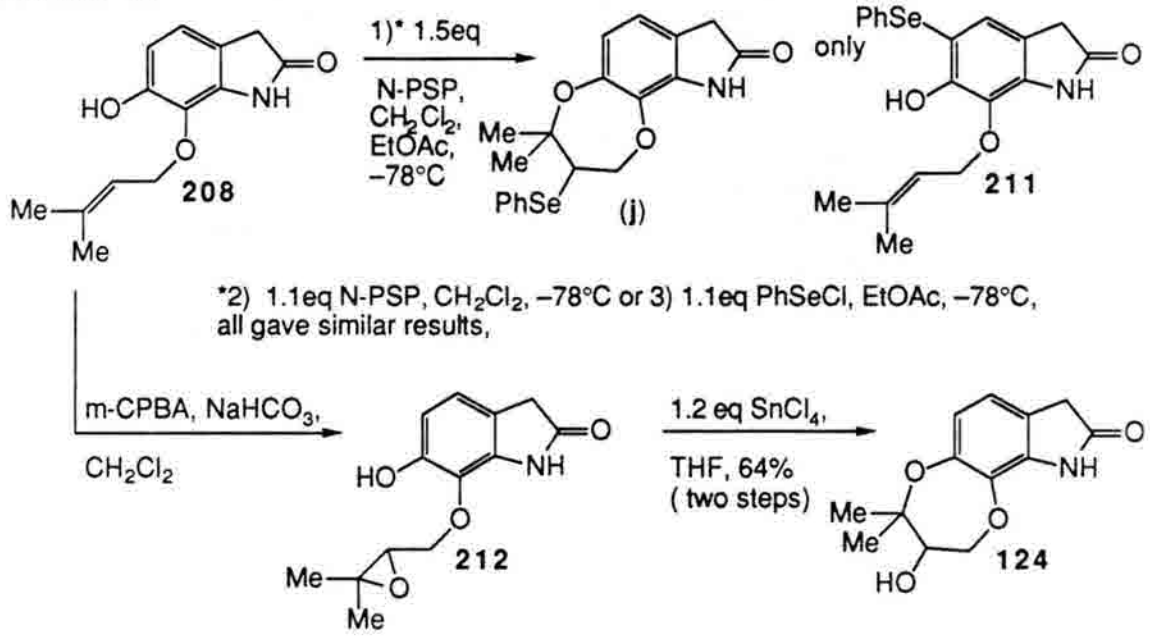
Scheme 54



Following the same procedure that was successful in the three previous examples, the prenylated substance **208** was subjected to the phenylselenoetherification conditions. Unfortunately with this substrate, the only product isolated was the selenide **211** (Scheme 55). This is not entirely surprising. In the simple model study employing catechol, this kind of electrophilic aromatic substitution product was also detected, and the oxindole **208** is even more electron rich than catechol. The alternative approach employing the

epoxidation and Lewis acid mediated cyclization was successful on this substrate although not entirely without difficulty. Again the reactivity of oxindole **208** mimicked the epoxidation reaction of the other prenylated phenols. The reaction had to be buffered with sodium bicarbonate in order to soak up the m-chlorobenzoic acid produced, to prevent the epoxide **212** from reacting with the phenolic group. The major by-product was the six-membered ring tertiary alcohol **213**. In most cases the reaction was worked up and taken on to the next step without any chromatography. In this way **211** was treated with tin tetrachloride in THF to provide the seven-membered ring alcohol **124** [77] (Scheme 55).

Scheme 55

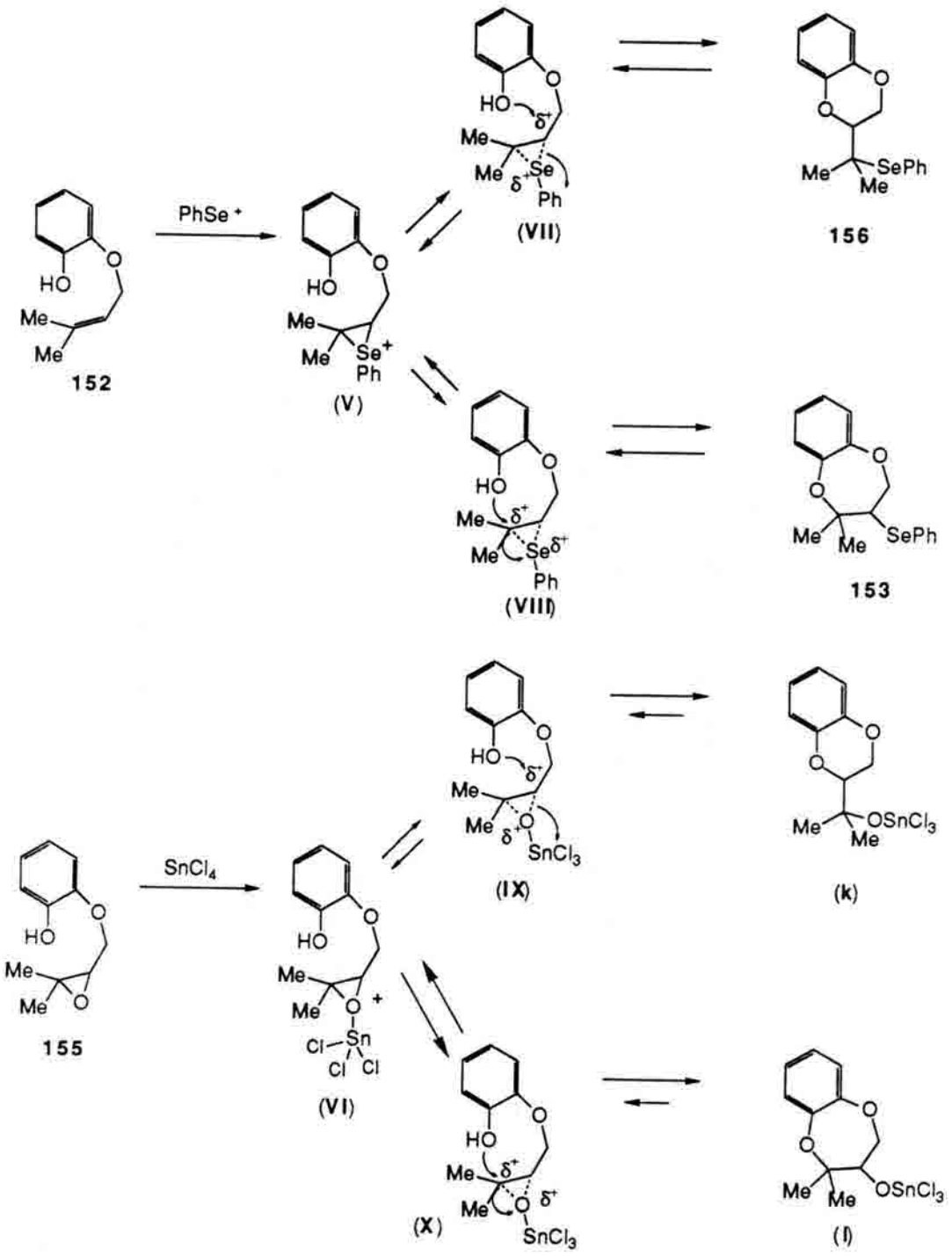


It is worth discussing the mechanism of these two very similar cyclization reactions. It is believed [78] that the phenylselenoetherification reaction occurs by way of the three-membered ring selenium species **V** (Figure 3) that subsequently endures an S_N2 nucleophilic attack by the phenol. It is the S_N2 character of this reaction that can effectively limit the seven-membered ring formation. Paradoxically, it is known that these reactions generally favor Markownikoff addition. However, it is also likely that this reaction is reversible and that the thermodynamically more favorable product is the six-membered ring selenide. Additionally, it has been reported that six-membered ring formation for this type

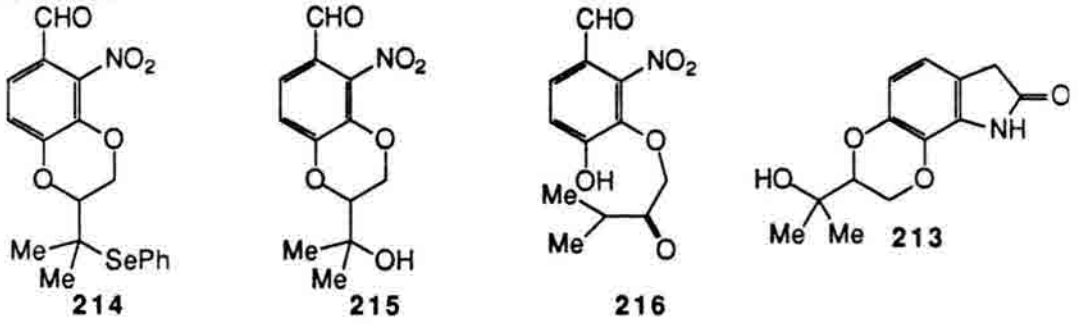
of reaction is favored over seven-member rings. This is probably due to angle strain and unfavorable steric interactions in the transition state, summarized by Baldwins rules.[79] The 6-*exo*-tet ring closure is more favored than the 7-*endo*-Tet. The best yields were obtained on the phenols **181** and **191** when CSA was added to increase reactivity of the seleneum reagent by protonation of the phthalimide, thereby increasing the leaving group ability. The increase in yield could simply be due to the fact that a manifestation of the competing electrophilic aromatic substitution reactions being minimized due to the deactivating nitro group; in the reaction of **208,** this was the dominant pathway. The stannic chloride mediated cyclization of an epoxide is very similar mechanistically to the phenylselenoetherification reaction, except that the seven-membered ring formation competes somewhat more successfully than six-membered ring production. This is most likely because under the reaction conditions, intermediate **VI** is more polarizable leading to the intermediate tertiary carbocation, and/or the reaction is less reversible than the phenylselenoetherification since, the O-$Sn(Cl)_3$ group is less nucleophilic than the phenylselenide group. This reasoning is supported by the prevalence of the six-membered ring byproduct **213** in the epoxidation step. Without the buffering bicarbonate, the main product was **213** (Figure 3).

Among the many side products of the phenylselenoetherification reaction the most obvious was the six-membered ring selenide, e.g.**156** and **214**, but there were other products as well. A commonly described byproduct is diphenyl diselenide, and this was encountered in all of the selenium reactions performed. There were products associated with addition across the double bond, and electrophilic aromatic substitution products such as **211**. As was mentioned before, the main byproduct of the stannic chloride mediated cyclization were the ketones resulting from a 1, 2-hydride shift, for example **216**. Interestingly, there was no ketone formed in the reaction of the oxindole **212** (Scheme 56).

Figure 3

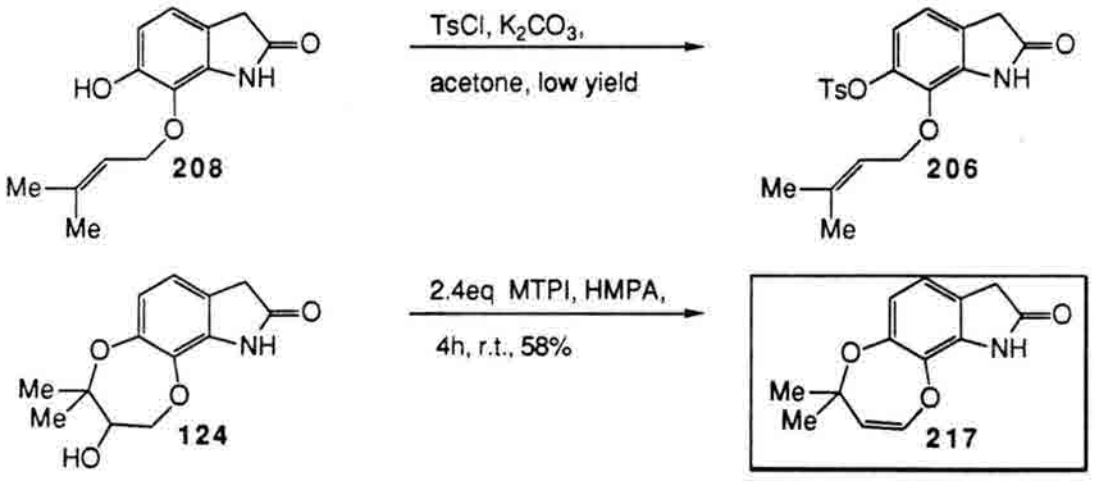

PhSe+
HO
Me
Me
152
Se+
Ph
(V)
δ+
Se
Ph
(VII)
SePh
156
Se δ+
(VIII)
153
SnCl4
155
Cl
Sn
Cl Cl
(VI)
SnCl3
(IX)
OSnCl3
(k)
(X)
(I)

Scheme 56



The question still remained about the absolute structure of the prenylated compound **208** (and **124**). Certain spectral characteristics pointed to the prenyl group being on the 7-position but, we were not sure that what was thought to be **208,** was not in fact the undesired isomer **209**. The proof was easily obtained by simply tosylating **208** and comparing the product to the previously prepared **206.** The two independently synthesized products were identical in every way. With the oxindole **124** firmly in hand, we decide that it would be interesting to eliminate the secondary alcohol, to supply us with the unique dioxepin–oxindole **217** (Scheme 57).

Scheme 57



This was done as before with MTPI in HMPA. We had hoped that perhaps this compound (**217**) might be biologically active but, a preliminary screening of this material showed no activity [80] (Table 7).

Table 7

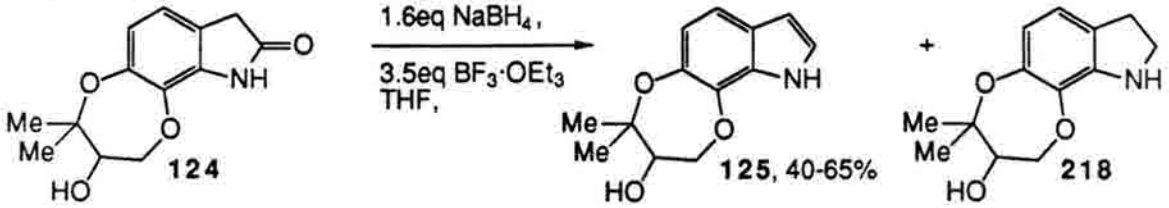
Microorganisms	Concentration of 217				
	10 mg/mL	1 mg/mL	0.1 mg/mL	10 μg/mL	1 μg/mL
Bacillus subtilis	R	R	R	R	R
Staphylococus aureus	R	R	R	R	R
Micrococus luteus	R	R	R	R	R
Candida albicans	R	R	R	R	R
Saccharomyces cerevisiae	R	R	R	R	R
Escherichia coli	R	R	R	R	R
Klebsiella pneumoniae	R	R	R	R	R
Serratia marcescens	R	R	R	R	R
Pseudomonas aeruginosa	R	R	R	R	R

R = resistant; no zone of inhibition

The next problem was to reduce the oxindole **124** to the indole. There are a number of reported ways to perform reductions on N-alkylated oxindoles. In the synthesis of sporidesmin,[81] the conversion of an N-methylated oxindole to the indole was accomplished with DIBAL. N-Alkylated oxindoles are also reported to be reduced to indoles by the use of $LiAlH_4$;[82] however, in the case of unsubstituted oxindoles, this reduction either fails or it requires forcing conditions (refluxing dioxane). Other methods include passage over hot zinc, or conversion to the thiooxindole followed by electrochemical desulfurization. A few other methods are reported, but by-and-large they are specific only for substituted oxindoles. In 1972 Plieninger [83] reported that substituted and unsubstituted oxindoles could be reduced to the corresponding indole in high yields with borane in THF at 0 °C. This contradicted another report about the reducing abilities of borane toward various indoles.[84] In that report, only traces of indole were found. This result echoed an earlier study [85] that essentially reported a similar observation (4% yield of indole from oxindole). So with a degree of trepidation we attempted the reduction of **124**, by following the procedure of Plieninger. The oxindole **120** was treated with BH_3 in

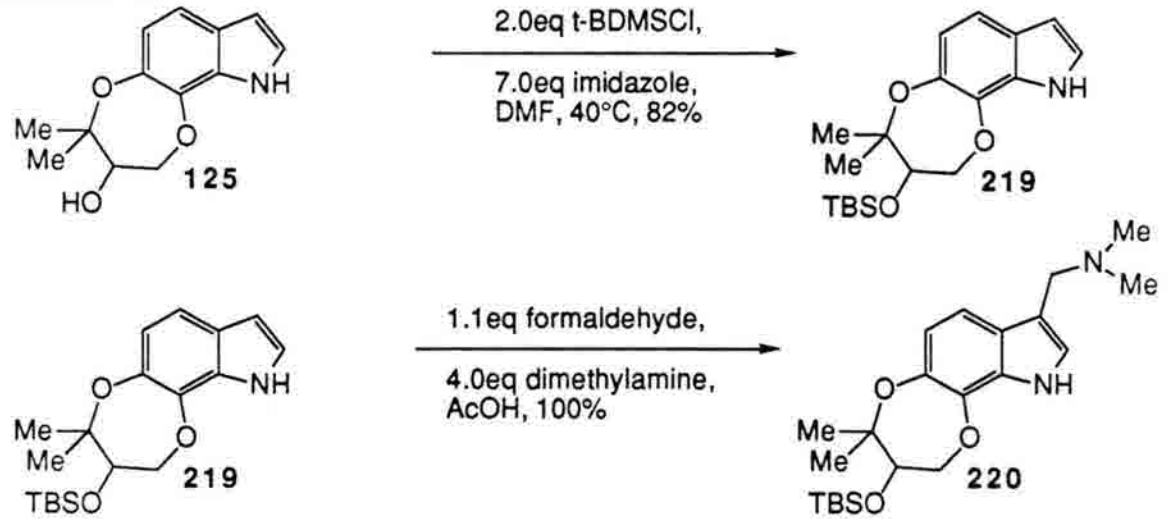
THF, but after five days there was no reaction. Oxindole **124** and **206** were both exposed with the same reaction conditions, but again only starting material was found. In these reactions we were using the commercially available BH_3 (1.0M BH_3/THF, Aldrich), but Plieninger had probably used borane that is generated prior to use by the reaction of $NaBH_4$ and $BF_3{\cdot}OEt_2$. In an attempt to mimic this reactivity, we treated oxindole **120** with $BF_3{\cdot}OEt_2$ and $NaBH_4$ in THF, resulting in a mixture of starting material, the desired indole and also some indoline. This was encouraging. When oxindole **124** was treated with 1.6eq of $NaBH_4$ and 3.5eq $BF_3{\cdot}OEt_2$ in THF for 1 day (0 °C to r.t.) the desired indole **125** was obtained in 50% yield. Oxindole **217** was also exposed with the same reaction conditions, but in this case no desired product was found. It appeared that the olefin in the dioxepin ring was being reduced. This was an interesting result because it implied that borane is being generated in the reaction; however, when **120** was subjected to a solution of BH_3 and $BF_3{\cdot}OEt_2$ in THF there was no reaction. It was reported [85] that when indole was treated with borane and quenched with water, the saturated indoline was the main product. In contrast, if the reaction was quenched with acetone, only unreacted starting material was recovered. When the crude reaction mixture of **124**, $BF_3{\cdot}OEt_2$ and $NaBH_4$ was quenched with acetone instead of water no product except unreacted starting material was found. All this implies that both the indole and oxindole reductions are complexed to the reducing agents in a similar manner. It stands to reason that there is some borane generated in the reaction, and it is probably complexed to the oxindole nitrogen. At the same time it appears that it is the Lewis acid properties of $BF_3{\cdot}OEt_2$ that activate the oxindole to reduction. Thus, it is the $NaBH_4$ or a similar species that actually does the reduction. Strangely, Biswas and Jackson [85] reported the reduction of oxindole by the same procedure we used, but they found no indole at all, only the over-reduced indoline in 85% yield. They substituted $LiBH_4$ for $NaBH_4$ (Scheme 58).

Scheme 58



In an attempt to improve the conversion of indoline **218** to **125**, compound **218** was stirred with a catalytic amount of salcomine and bubbling in O_2; unfortunatly, no reaction occurred. This was disappointing, considering the ease with which various halogenated indolines were converted to the indoles by this procedure.[86] In any event, the protection of the secondary alcohol of **125** was required prior to the Somei/Kametani alkylation. We picked the ubiquitous *tert*-butyldimethylsilyl group, since it is easy to remove, and can withstand many different conditions. The reaction of the indole **125** with t-BDMSOTf gave many different products, including the O-silyl, and N-silyl-indole, but only a poor yield (19%) of the desired material. However, when the indole **125** was treated with a warm solution of t-BDMSCl and imidazole in dimethylformamide, the conversion to the required o-silylindole **219** was quite good. Heating was required because of the hindered nature of this particular alcohol. Indole **219** was easily converted to the gramine **220** through the well known Mannich procedure (Scheme 59).

Scheme 59



Thus, the synthesis of **220** was 14 steps from vanillin in an overall yield of 2.5%. Even though this was not a spectacular yield, the synthesis did fulfill a number of the original criteria. Chromatography was only necessary in four of the 14 steps and it wasn't until the ninth step that the first column was employed. This allowed us the ability to prepare large quantities of **220** in order to carry the total synthesis further.

CHAPTER THREE

THE TOTAL SYNTHESIS OF (+)-PARAHERQUAMIDE B

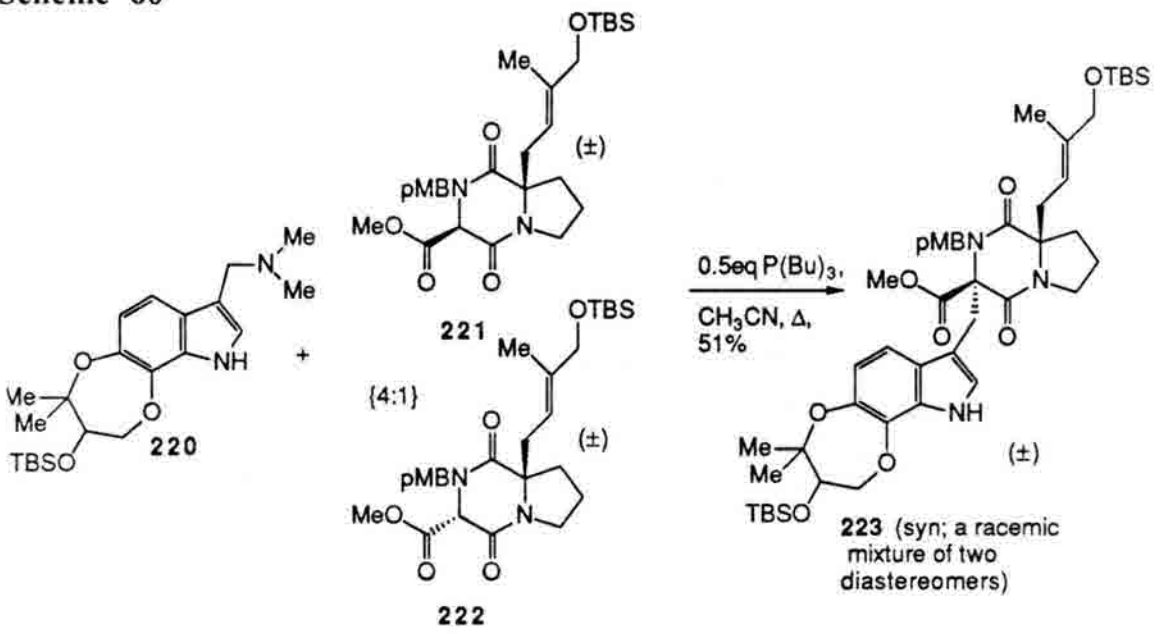
"the successful outcome of a synthesis of more than 30 stages provides a test of unparalled rigor...of the predictive capacity of the science"

R. B. Woodward

3.1 Model for the Total Synthesis of the Paraherquamides

There was a fairly large supply of racemic piperazinedione **93** (**221**&**221**) left over from the synthetic work on brevianamide B. We thought it would be advantageous to use this, and the gramine **220** to model the total synthesis of the paraherquamides. This would give us much useful information for the actual synthesis. The coupling of these two pieces proved successful. The yield of the desired product **223** was consistently between 51–56% (Scheme 60).

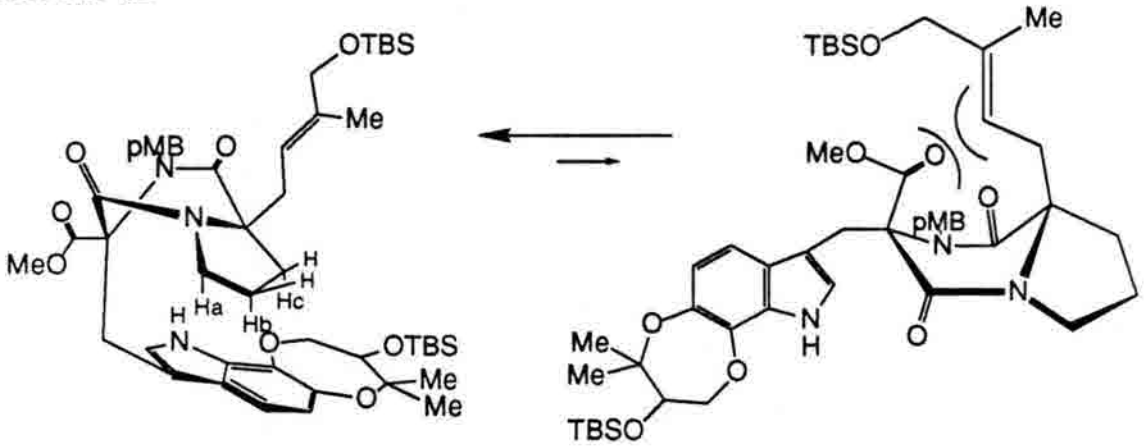
Scheme 60



This was only a few percent lower than what was obtained in the brevianamide synthesis. It is an interesting reaction. In the brevianamide B synthesis Williams *et al.* [24c,d] reported only one diastereomer, *syn*-**94** (the methylcarboxylate takes precedence over the larger indole). They noticed a large upfield shift of two proline ring protons (δ 0.0, 0.45 ppm). The methyl carboxylate is sterically congested by the bulky isopentenyl group, forcing the indole down and under the piperazinedione, effectively shielding the two protons by the indole ring; of course the *anti*-isomer could not adopt this conformation. This is confirmed by a consideration of the mechanism of the Somei/Kametani reaction. According to that mechanism,[39,87] the bulky tributylphosphinoindole could only approach

from the less congested face of the piperazinedione enolate. The same phenomenon was observed in the reaction of **221**, **222** and **220**. There was a large upfield shift of the proline ring protons of **223** (δ Ha, Hb; 0.034–0.19 (m), 0.43-.52 (m) ppm) (Scheme 61).

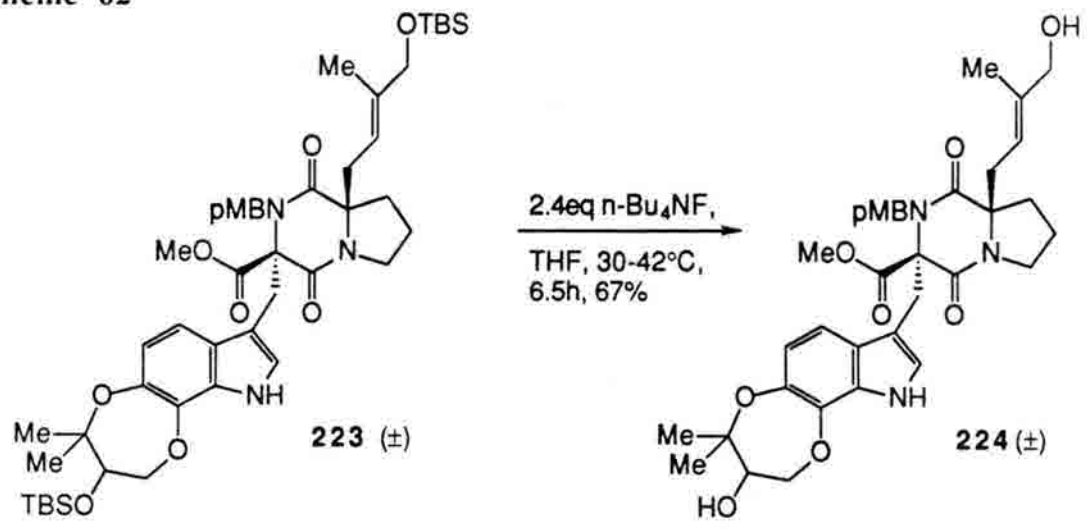
Scheme 61



(XI) **(XII)**

We thought it prudent to desilylate to simplify the nmr spectrum, because the product of this reaction was a mixture of racemic diastereomers. Therefore, **223** was treated with tetra-n-butylammonium fluoride providing the diol **224**. This compound had a simpler spectrum and the three high field protons were easily discernible (δ 0.10–0.199 (m), 0.51–0.68 (m), 0.85–0.96 (m) ppm) (Scheme 62).

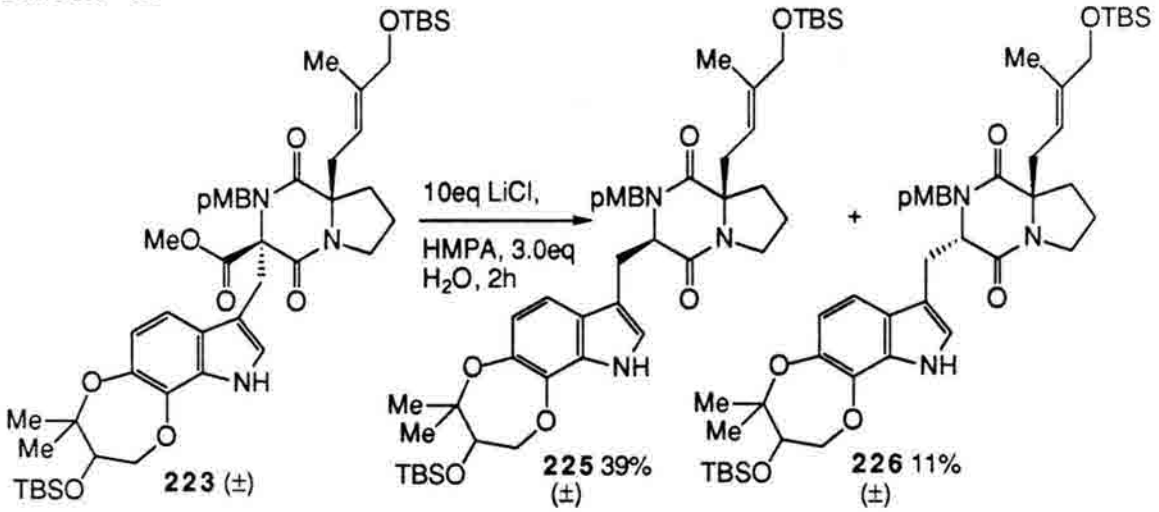
Scheme 62



The next step was the decarbomethoxylation of **223**. This reaction was fairly clean, although there was some recovered starting material. The two products isolated

were the *syn*-isomer **225** and the *anti*-isomers **226** isomers, in a ratio of 3.3 : 1.0. The structural assignments were made by comparing the Rf values and spectral characteristics with the corresponding brevianamide precursors. The starting material **223** was the least polar (Rf = 0.38), the *syn*-compound **225** was the most polar (Rf = 0.08), and the *anti*-isomer **226** had an Rf of 0.21. The relative polarity of the *syn*- and *anti*-diastereomers as identical to that found for other proline-containing piperazinediones. Westley [88] found that of various piperazinediones, the *syn*-isomer was the least polar. This was also echoed by both Kametani [87] and Kishi/Hutchison.[13] Additional evidence supporting these structural assignments came from an upfield shift of three proline protons in product **226**, a shift that is entirely lacking in the other diastereomer. This is interesting, because the prolino ring protons of **226** are indeed shifted upfield (δ 0.26–0.41 (m), 0.47–0.58 (m), 0.62–0.72 (m) ppm), but they are not quite as high as the ring protons of **223**. This is understandable considering that **226** is not encumbered with the carbomethoxy group and therefore has considerable more **XII**- like character (Scheme 61). Theses ideas will be explored more deeply in the next section (Scheme 63).

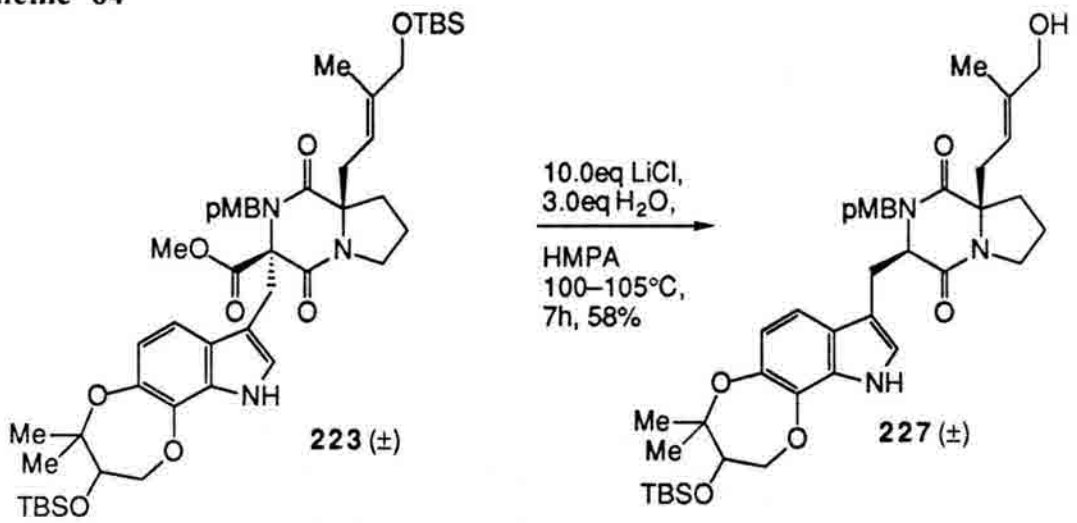
Scheme 63



The decarbomethoxylation reaction was repeated in an attempt to increase the conversion. This was done exactly as before, but the time was increased to seven hours. The result was not encouraging. While the yield improved slightly (58%), the only product

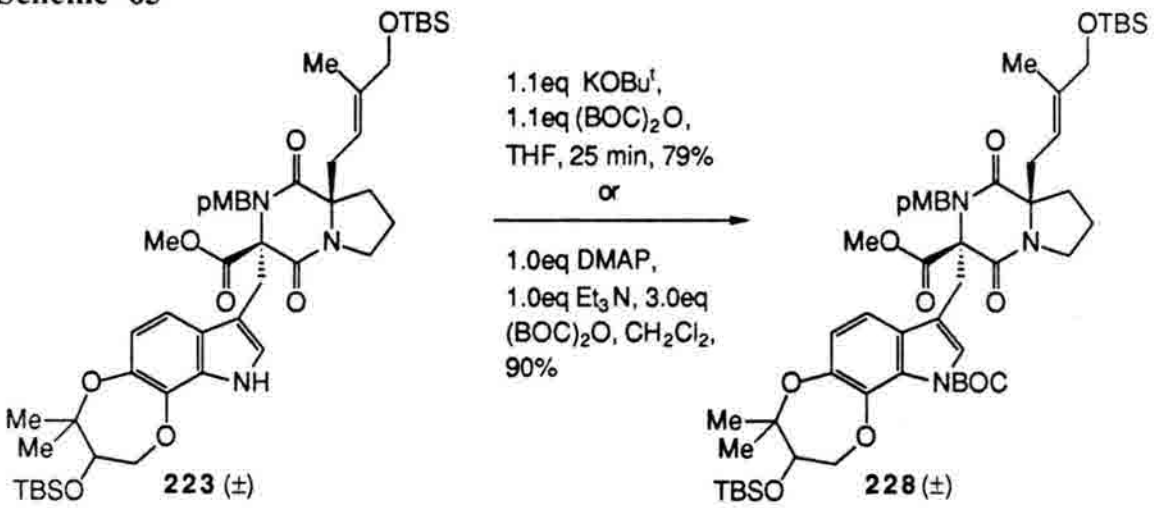
isolated was the *syn*-diastereomer, and it had lost the allylic t-butyldimethylsilyl group. This product (**227**), was useless for our purposes (Scheme 64).

Scheme 64



At this stage the indole still needed to be protected before the S_N2' cyclization could be attempted. It seemed likely that the sensitive allylic alcohol would interfere with the indole nitrogen. We decided to block the indole nitrogen of **223** and then try the decarbomethoxylation reaction, with the aim of obtaining an allylic alcohol like **227**. This would mean one less step in the synthesis. The indole **223** was blocked using di-*tert*-butyl dicarbonate and potassium *tert*-butoxide providing the fully protected compound **159**. This reaction was repeated numerous times and the yields varied from quantitative to very poor. The reasons for the poor conversion were never fully determined, but the product isolated in these cases appeared to be polymeric in appearance. Apparently the compound interacts with some impurity in the potassium *tert*-butoxide. There was some indication that the methyl carboxylate played a role, because no problems were ever encountered when this group was lacking. We therefore tried an alternative method. This involved treating the substrate **223** with 4-dimethylaminopyridine, triethylamine, and di-*tert*-butyl dicarbonate in dichloromethane.[89] The yield of **228** was good (90%), and the reaction itself was easier to perform (Scheme 65).

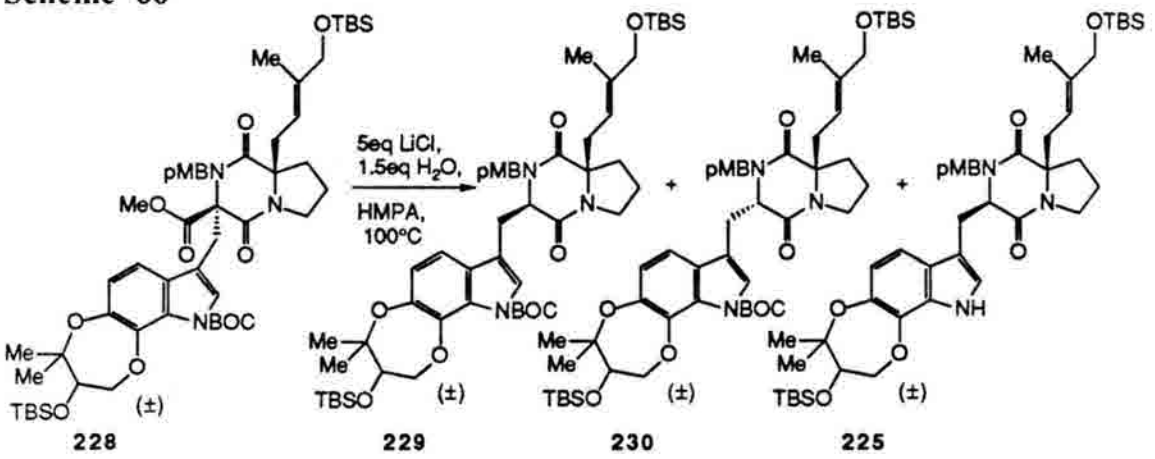
Scheme 65



The decarbomethoxylation was then done on the fully protected **228**. Surprisingly, the ratio of *syn*-to *anti*-diastereomers changed considerably. Compound **228** was treated with five equivalents of lithium chloride, 1.5 equivalents of H_2O in HMPA at 100 °C for 1 hour and 15 minutes. The yield was 88%; **229** (*syn*-, 66%), **230** (*anti*-, 3%) and **225** (*syn*-,minus the BOC group, 19%). The product distribution changed again, when the reaction was repeated for 1.5 hours. The yield was 84.5%, **229** (*syn*-, 50%), **230** (*anti*-, 4.7%) and **225** (28%). Apparently, the *tert*-butoxycarbonyl group is lost after the decarbomethoxylation; therefore the idea of thermally removing the allylic O-silyl group at the same time was discarded. Again, the ratio of *syn*- to *anti*-diastereomers had increased dramatically. Taking into account the loss of the *tert*-butoxycarbonyl group the *syn*:/*anti* ratio has grown to >16:1. The polarities of these compounds did not change relative to the previous group (**223**, **224**, **225**). The *syn*-isomer **229** was considerably more polar than the *anti*- **229** and the starting material was again the least polar (Scheme 66).

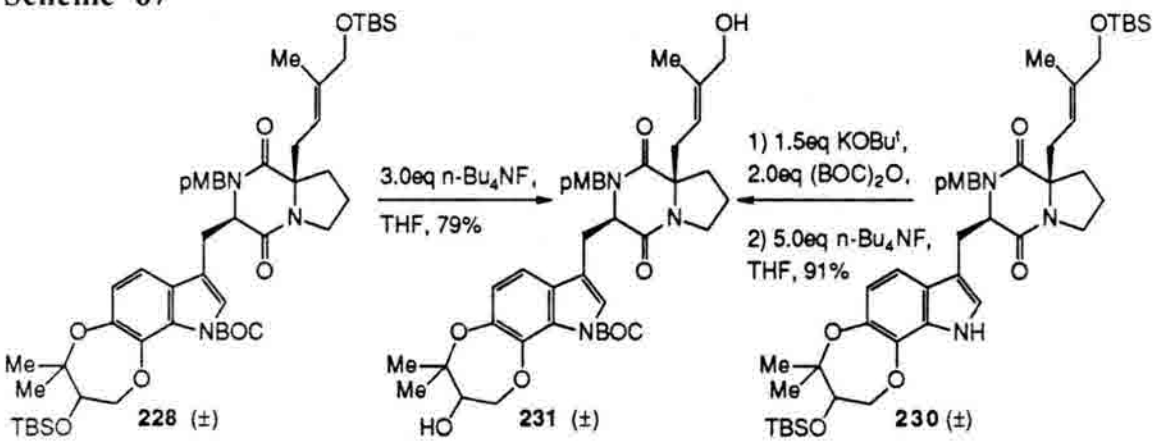
Compound **229** was deprotected with tetra-n-butylammonium fluoride to provide the diol **231**. We found that the allylic alcohol of **229** could not be selectively deprotected in the presence of the hindered secondary alcohol. Treatment of **229** with one equivalent of tetra-n-butylammonium fluoride resulted in three products; it seemed that the rate of

Scheme 66



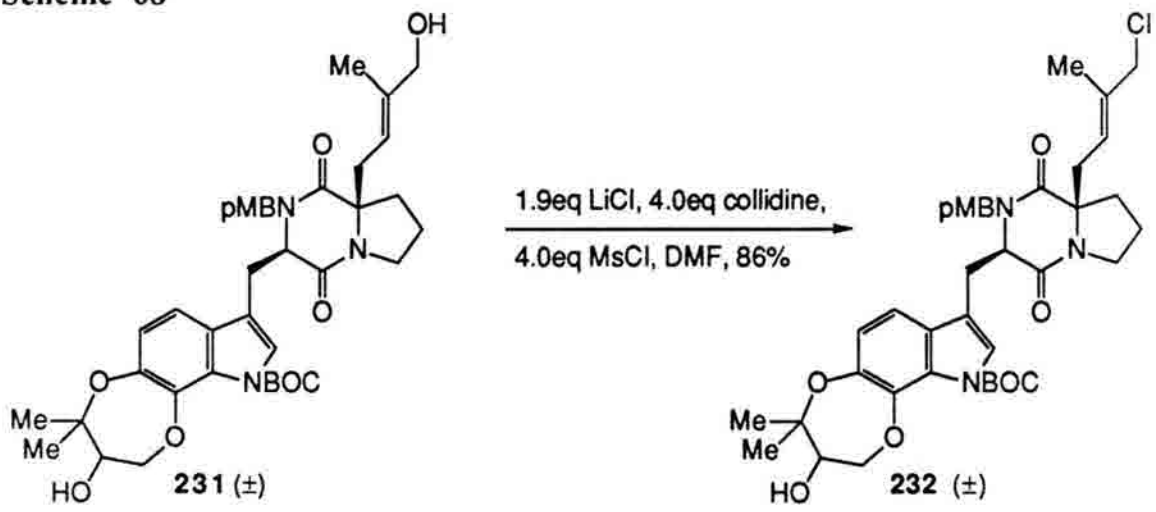
desilylation of the two groups was very close. The other product (**225**) was also converted to **231** by sequential treatment with di-*tert*-butyl dicarbonate, followed by tetra-n-butylammonium fluoride. This one pot, two step procedure worked quite well; there were no problems with the potassium t-butoxide in this case (Scheme 67).

Scheme 67



The diol **231** was converted to the allylic chloride **232** in 86% yield,. However, the reaction was sluggish and if worked up to soon, intermediate products (mesylates) were isolated (Scheme 68).

Scheme 68



Now, it was time to try the S_N2' reaction. It was possible that the free alcohol would not unduly affect the cyclization, providing there was an excess of base used. The chloride **232** was refluxed with ten equivalents of sodium hydride for 2.5 days, until the starting material was gone. Four products were isolated but none of them was the desired bicyclo [2.2.2] product. The major product was the unusual 12-membered macrocycle **233**, obtained in a surprising 35% yield. This type of compound is not unprecedented. During the course of the synthetic work on brevianamide B, the corresponding macrocycle was isolated in 13% yield. The reaction conditions were almost identical, but in the former reaction, they isolated the desired bicyclo [2.2.2] product (**100**) in 82% yield (Scheme 69), (Figure 4).

Scheme 69

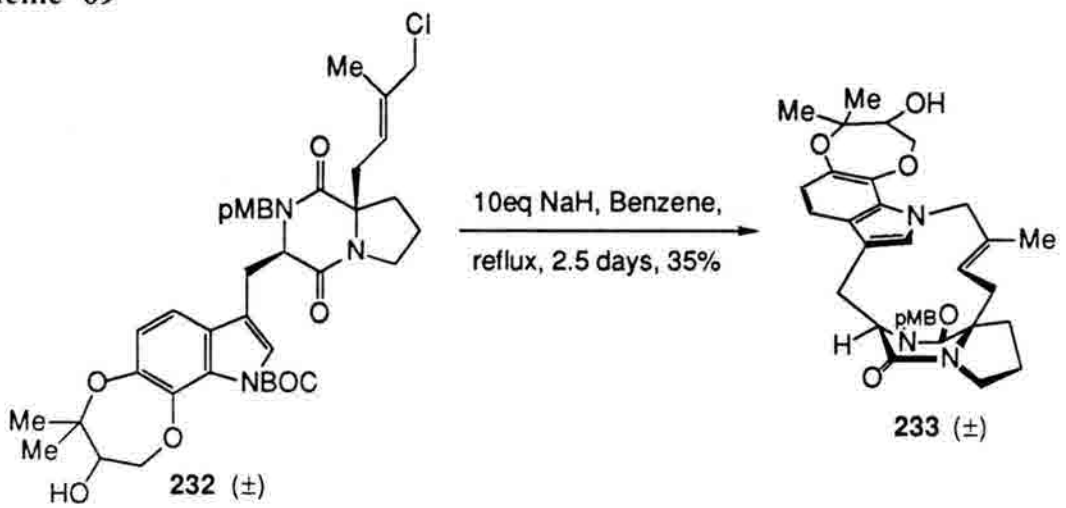
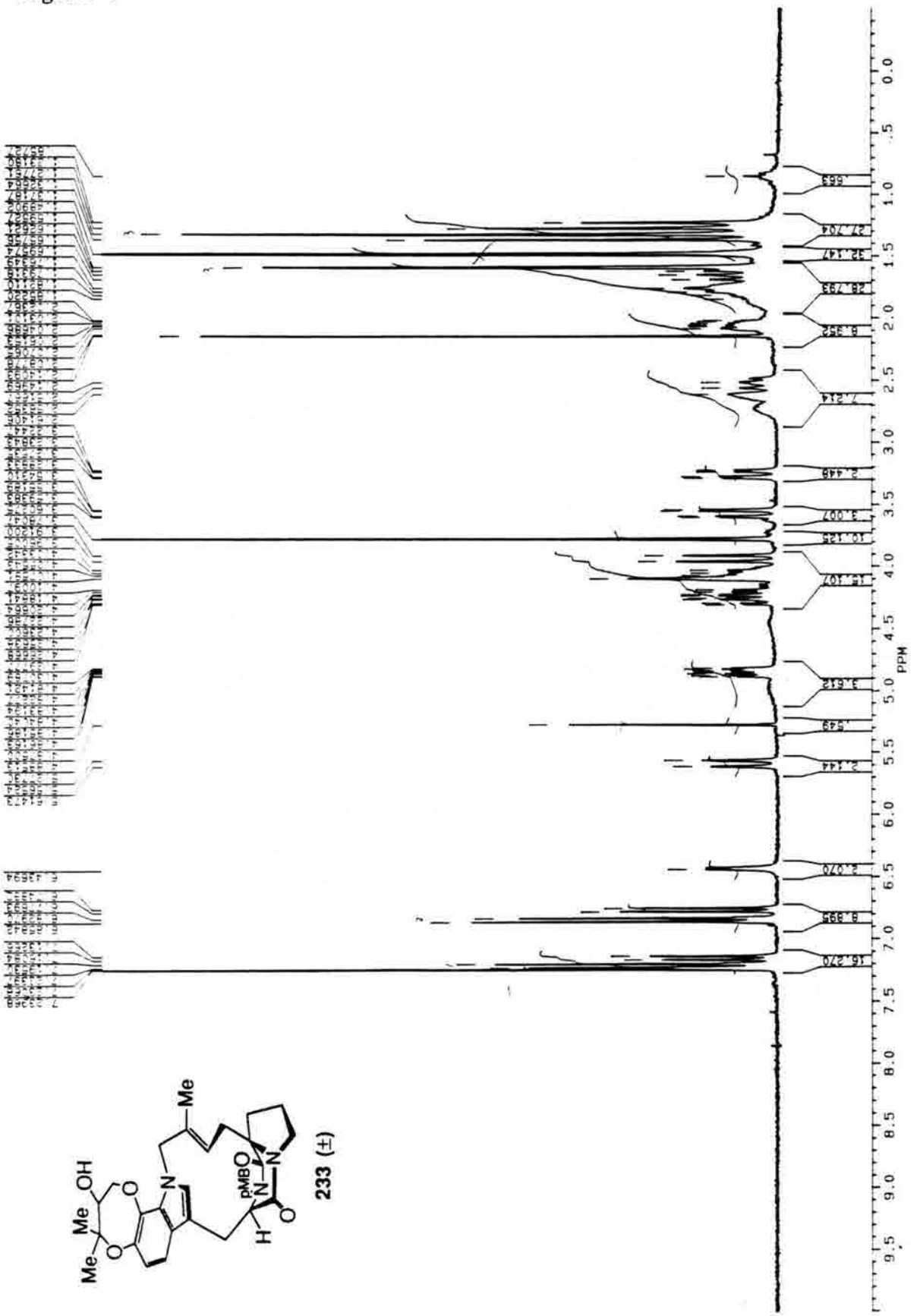
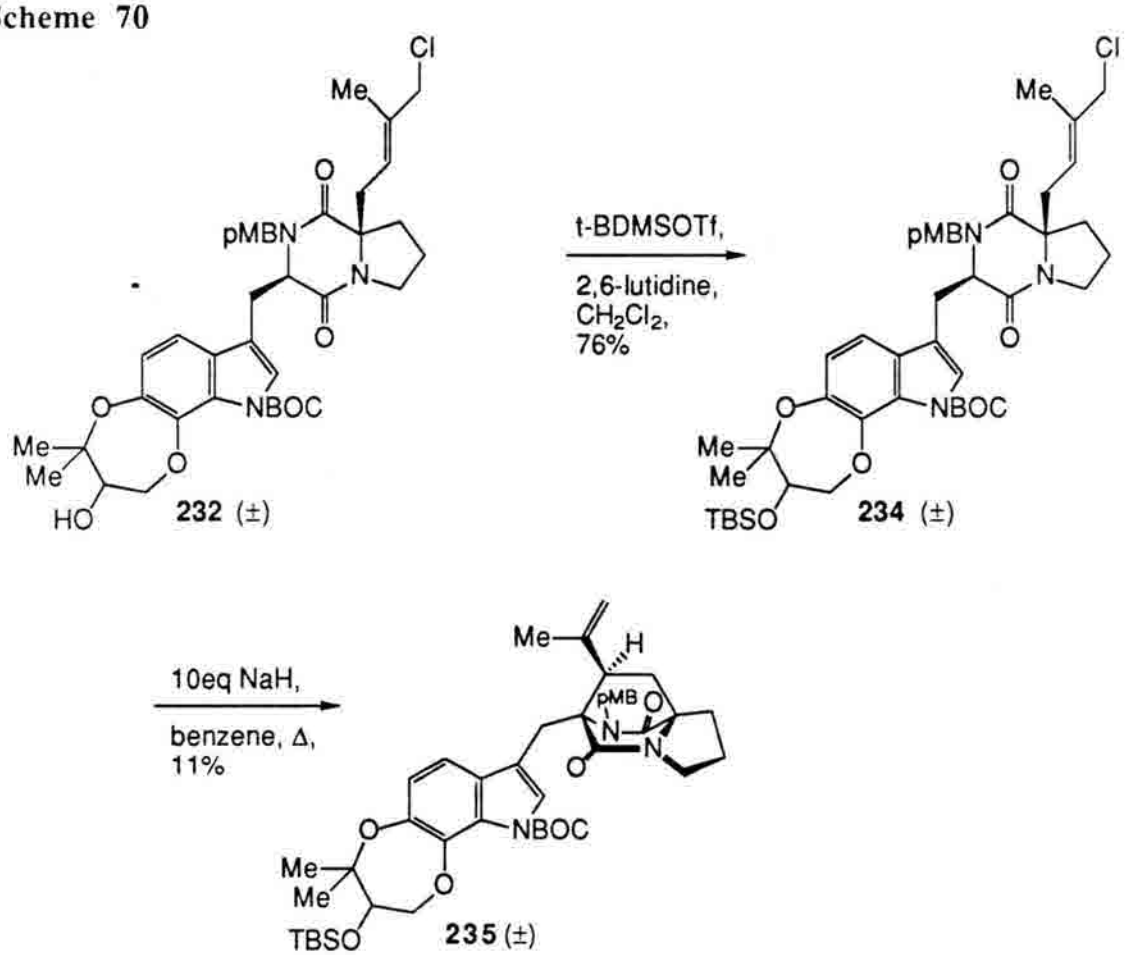


Figure 4



We decided that it might be important to reprotect the secondary alcohol of **232**. However, treatment of **232** with t-BDMSCl and imidazole in dimethylformamide at 50 °C caused slow decomposition, while t-BDMSOTf in 2,6-lutidine and dichloromethane gave the desired product **234** in 76% yield. There was some concern about this reaction because of the known reactivity of the t-butoxycarbonyl group with the t-butyldimethylsilyltriflate; the BOC group undergoes transesterification quite readily.[90] This problem was minimized by carefully treating **232** with a minimal amount of t-BDMSOTf. Compound **243** was subjected to the same conditions as before (10eq NaH, refluxing benzene), but the reaction proved extremely sluggish. After five days at reflux and eight more days at room temperature, the reaction was worked up. The desired product **235** was obtained in only 11% yield (Scheme 70).

Scheme 70

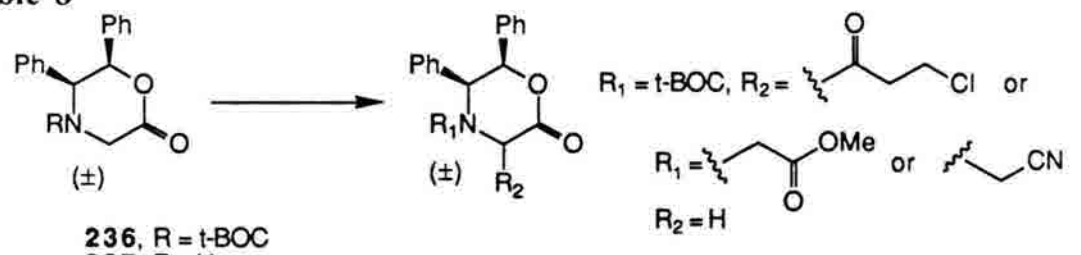


Surprisingly, there was not a trace of the macrocycle product. Additionally, the reaction appeared totally stereoselective. Recall that when **95** was refluxed with sodium hydride in benzene, the ratio of products (**100/96**) was 97:3. The "*endo*-" isomer (**100**) had the wrong relative chemistry for the brevianamide synthesis, but it had the correct one for the paraherquamides (Scheme 30). Compound **235** is in the "*endo*-" configuration. The corresponding "*exo*-" product was never detected, this was determined by a comparison of proton nmr spectra of **235**, **100**, and **96**. The poor yield confirmed some of our suspicions about this reaction. The difference between starting material **234** and the corresponding brevianamide precursor **95** is the large increase in the steric bulk of the indole moiety, obviously affecting the rate of reaction. In an attempt to overcome this problem, we tried to prepare the allylic bromide from the diol **232.** Treatment of **232** with triethylamine and methane sulfonylchloride followed by LiBr in acetone gave a single spot by TLC. After workup, this proved to be at least 3 compounds; a mixture of mesylate and bromide products. No attempt was made to take these on to the S_N2' step, because it was highly probable that the mesylate or bromide would be too reactive for the silylation step anyway. The failure of this approach left us one alternative: we had to replace the bulky p-methoxybenzyl group. This was something that we had planned for. Since in the brevianamide synthesis, removal of the p-mb group proved to be a major difficulty. These ideas were uppermost in our mind when we embarked on the synthesis of the piperazinedione portion of paraherquamide A (see Scheme 32).

3.2 Approaches to the Methyl,Hydroxy-Proline of (–)-Paraherquamide B

The first task was to obtain the deprotected lactone **237**. Treatment of the racemic lactone **236** with trifluoroacetic acid provided the required amine **237** in 91% yield. We started with the racemic version of **109** as a model. These lactones (**236** and **237**) were subjected to various alkylating agents; methyl acrylate, acrolein, and 3-chloro chloropropionate. In no case was the desired alkylated amine ever found (Table 8)

Table 8



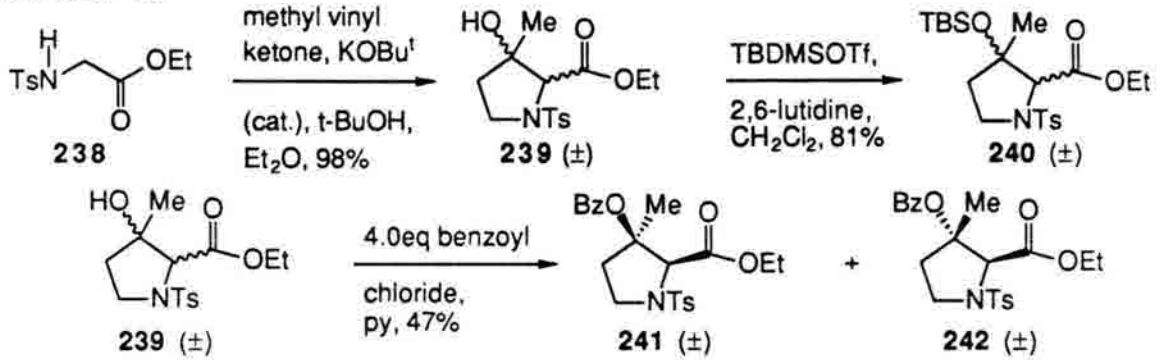
236, R = t-BOC
237, R = H

entry	reactant	conditions	outcome
1	**237**	1.0eq NaH, methyl acrylate, DMF	no desired product
2	**237**	1.2eq acrylonitrile, EtOH, reflux	starting material, no recognizable product
3	**237**	20eq methyl acrylate, EtOH, reflux, 12h	decomposition
4	**237**	1.0eq NaH, 1.1eq, methylacrylate, DMF,–46 °C - r.t. 7h	no recognizable product
5	**237**	2.0eq NaH, 1.0eq methylacrylate, THF, –78 °C - 0 °C, 14h	no reaction (–78 °C), decomposition at r. t.
7	**236**	5.0eq chloro 3-chloropropianate, 1.5eq $LiN(SiMe_3)_2$, THF, HMPA	no recognizable product
8	**236**	1.0eq NaH, 1.1eq methyl acrylate, THF, –42 °C, (2h) - r.t. (2h)	no reaction
9	**236**	2.0eq triethylamine, 1.1eq 3-bromo ethyl propionate,THF,r.t. - reflux(10h)	no reaction
10	**236**	1.1eq 3-bromo ethylpropionate, 1 day	no reaction
11	**236**	1.5eq acrylonitrile, THF, 4 days	no reaction

Due to the failure of the above approach, we thought it desirable to develop some alternative strategies. One possible method, the synthesis of paraherquamide A in racemic form is outlined below (Scheme 71). Tosylated glycine ethyl ester (**238**) was easily prepared from the glycine ethyl ester hydrochloride salt. This protected material was condensed with methyl vinyl ketone, providing **239** in 98% yield,[91] as an inseparable mixture of diastereomers. In an attempt to determine the ratio of the desired diastereomer to

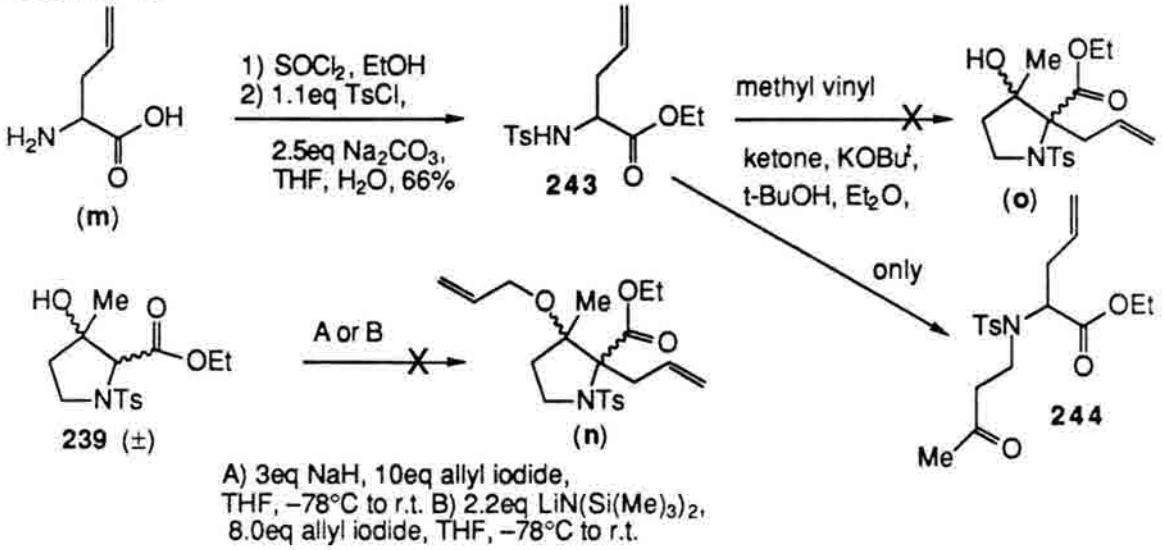
the undesired one, and to probe the reactivity of the tertiary alcohol, the proline **239** was protected with t-BDMSOTf, supplying **240** in 81% yield. Unfortunately, the silyl-protected diastereomers could not be separated. When **239** was protected as the benzoate, the diastereomers were separable on silica gel. These racemic diastereomers (**241** and **242**(desired)) were produced in a ratio of (3:4) (Scheme 71).

Scheme 71



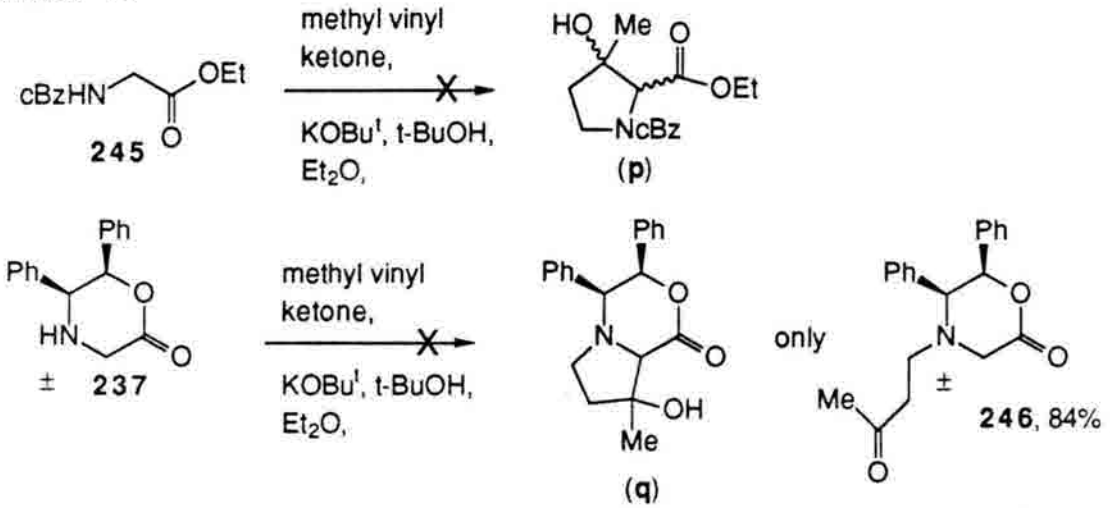
The mixture of isomers **239** was alkylated with an excess of allyl iodide. We hoped to alkylate the tertiary alcohol at the same time, since an allyl protecting group is easily removed (e.g. ozone). The diastereomers could then be separated, and converted in a few steps to a compound similar to **112** (Scheme 32). In spite of our efforts this alkylation failed. Apparently, the proline derivative is too sterically congested for the reaction to take place. To get around this problem we thought it might be easier to incorporate the allyl group prior to the cyclization. D,L-2-Amino-4-pentenoic acid was converted to the ethyl ester and N-tosylated in a two-step procedure in 66% yield. This compound (**243**) was subjected to the same cyclization procedure as before, but no proline product was ever found. The only material ever isolated was the N-alkylated derivative **244** (Scheme 72).

Scheme 72



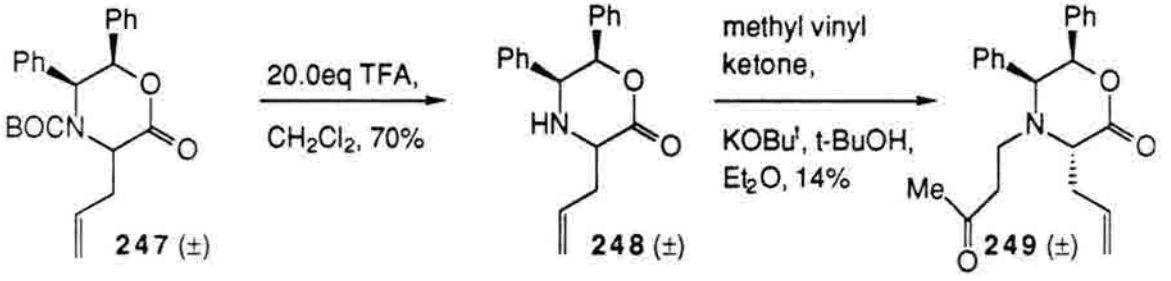
Besides these small setbacks, we were also concerned about the possible difficulties of removing the N-tosyl group. Most of the known methods for removal of this group are fairly harsh [92] or require special apparatus (electrolytic cleavage).[93] We thought that a carbobenzoxy protecting group would fit the bill, and the protected glycine **245** was easily prepared. Unfortunately, **245** did not condense with methyl vinyl ketone as hoped; some polymeric material was formed. Attempted alkylation of racemic oxazinone **237** with MVK gave a reaction product identified as **246**. Even though the cyclization did not take place, this seemed to be a good procedure for effecting the N-alkylation, providing the tertiary amine **246** in 84% yield (Scheme 73).

Scheme 73



The failure of the lactone **237** and the carbobenzoxy protected glycine **245** to cyclize with methyl vinyl ketone is probably due to the relatively high pK_a of the α– proton of the oxazinone. The strong electron withdrawing ability of the tosylate renders the α-proton of **238** to be sufficiently acidic. The allylated lactone was also prepared with the aim that the allyl group would exert some influence on the pK_a of the resulting methine proton. If the cyclization did not occur, perhaps the resulting N-alkylated compound might be more amenable to intramolecular condensation since, an attempt to cyclize **243** was a complete failure. This is not too surprising considering there are three possible enolates, all with similar pK_as. The previously prepared allylated *tert*-butoxycarbonyl protected lactone **247** was easily deprotected to provide the free amine **248**, but when this was treated with methyl vinyl ketone only a poor yield (14%) of the N-alkylated material **249** was found (Scheme 74).

Scheme 74



At this time our attention was turned to the paraherquamide B synthesis. Work on this had already been started as a side project. When Merck & Company reported the isolation of paraherquamides B–G, we ceased work on the paraherquamide A proline problem.

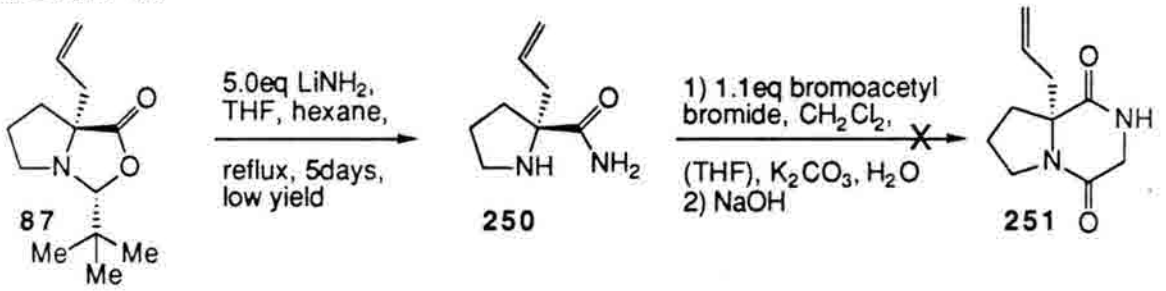
The first stereocontrolled total synthesis of (+)-paraherquamide B (**3**) is described in the next section.

3.3 The Total Synthesis of (+)-Paraherquamide B

Our initial approach was to modify the brevianamide synthesis avoiding the use of the recalcitrant *para*-methoxybenzyl group. In the brevianamide B synthesis, the allylated bicyclic compound **87** was opened up with lithio-*p*-methoxybenzylamine providing **88**

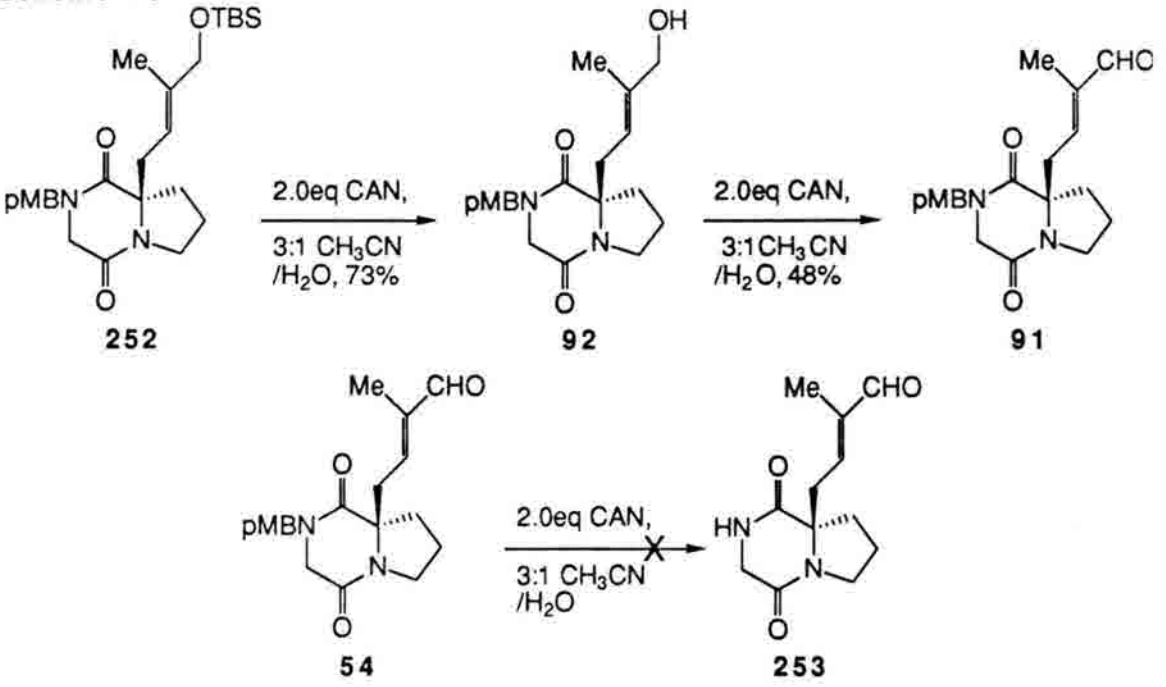
(Scheme 21). We decided to use lithium amide instead since, Seebach [94] has demonstrated the utility of this reagent in a similar amination; however, difficulties were immediately encountered with this reaction. The conversion was very poor and the prolinamide **250** was so polar it was hard to handle. The amide **250** was exposed with Schottan–Bauman conditions in an attempt to create the piperazinedione **251** (see Scheme 21), but no product was ever formed. This reaction was also tried in tetrahydrofuran with the same results (Scheme 75).

Scheme 75



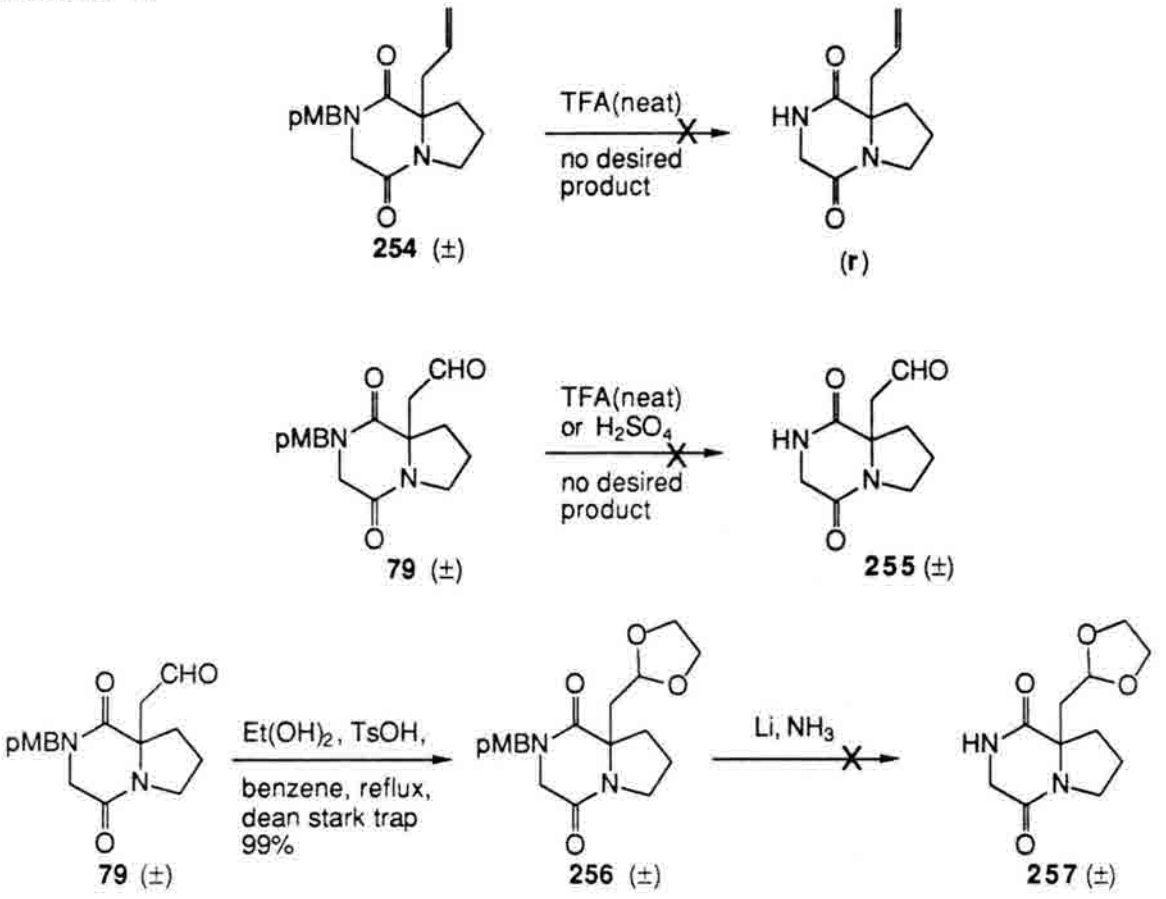
Due to the failure of the prolinamide synthesis another tact was tried. We envisioned that 2,4,6-trimethoxybenzylamine anion would effectively open up the bicyclic compound **87**, and this group is known to be much easier to cleave than the *para*-methoxybenzyl group.[95] However, this reaction did not work either. It seemed that the best approach would be to follow the synthesis of **91** (Schemes 27, 28) as closely as possible. This eight step protocol has a number of very attractive features: first, the reactions are all fairly high yielding; second, very little chromatography is needed and; lastly, all the reactions seemed to be amenable to large scale work. The main obstacle would be the removal of the *para*-methoxybenzyl group. In fact, during the later stages of the brevianamide B synthesis, when all methods at deblocking the penultimate products **97** and **98** were failing, a considerable effort was expended to remove this group much earlier in the synthesis. The primary focus was on deblocking the *para*-methoxybenzyl group with ceric ammonium nitrate. The reactivity of three substrates was explored; all of which were precursors in the brevianamide synthesis (see Scheme 28). The results are summarized below (Scheme 76).

Scheme 76



Unfortunately, none of the desired product was ever found. This was not encouraging. There was still a fair amount of racemic brevianamide precursors available to help us probe the feasibility of removing the *para*-methoxybenzyl group. So our initial efforts made use of alternative methods of deprotection. The olefin **254** was treated with trifluoroacetic acid,[96] but only decomposition products were formed. The aldehyde **79** was also treated with neat trifluoroacetic acid, but only a polymeric material was isolated. The same substrate (**254**) was treated with sulfuric acid [97] with similar results. Alternatively, the aldehyde **79** was converted to the acetal **255**, and then subjected to a dissolving metal reduction (Li, NH_3), but again, there were no recognizable products (Scheme 77).

Scheme 77

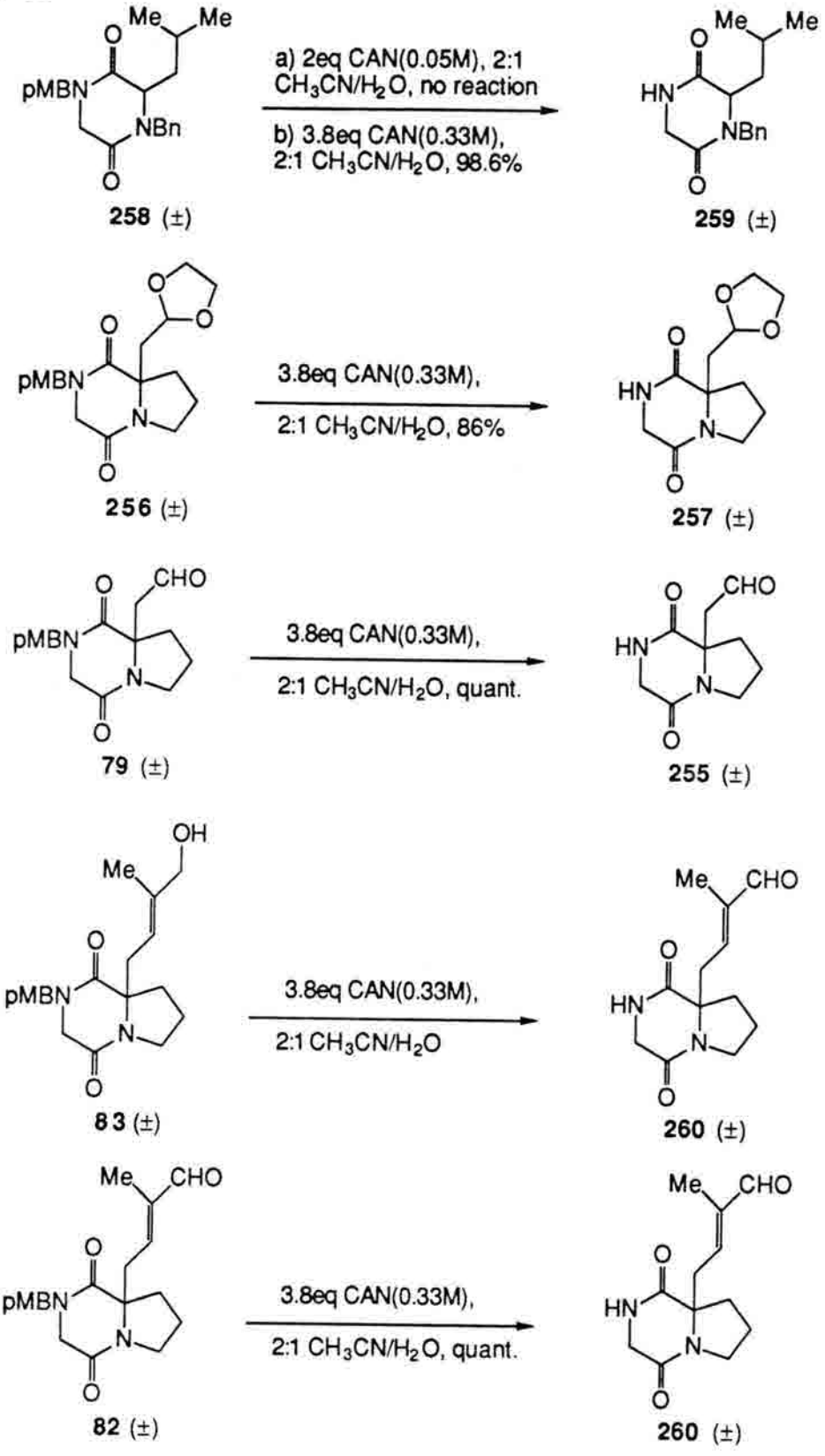


There are other reported methods to remove N-benzyl groups: Ca/NH_3,[98] $AlCl_3$,[99] Pd·C/HOOH [100] to name a few, but all these methods seemed to be incompatible with the system at hand. The most attractive method to effect cleavage of the *para*-methoxybenzyl group was still ceric ammonium nitrate.[101] A close reading of the original publication [101] led us to re-examine this approach. Yoshimura *et al.*. [101] found no reaction of the substrate **258** when it was treated with two equivalents of ceric ammonium nitrate(0.05M) in a 2:1 ratio of CH_3CN/H_2O for 3 days. However, when the exact same reaction was done with 3.8 equivalents of ceric ammonium nitrate(0.33M) in a 2:1 ratio of CH_3CN/H_2O, the reaction gave a 98.6% yield of **259** in only 2 hours. This indicates that this reaction is concentration dependent. A separate group, in a mechanistic investigation of the oxidative properties of this reagent(CAN) reached similar conclusions.[102] The previously prepared dioxolane **256** was treated with 3.8 equivalents of ceric ammonium nitrate (0.33M) in a 1:2

ratio of H_2O/CH_3CN providing in high yield the desired secondary lactam **257**. The same reaction was tried on the aldehyde **79** with a nearly quantitative yield of the deprotected aldehyde **255**. This same reaction was also tried on the alcohol **83** (racemic **92**). Interestingly, this gave primarily the deprotected and oxidized product **260** in stark contrast to the reaction of **92** that yielded **91** as the sole product (see Scheme 76). The success of the ceric ammonium nitrate reaction on these substrates was extremely encouraging. The same reaction was repeated again, but this time with the enal **82** (racemic **91**). Using 3.8 equivalents of ceric ammonium nitrate (0.33M) in a 1:2 ratio of H_2O/CH_3CN, the deprotected enal **260** was isolated in quantitative yield (Scheme 78).

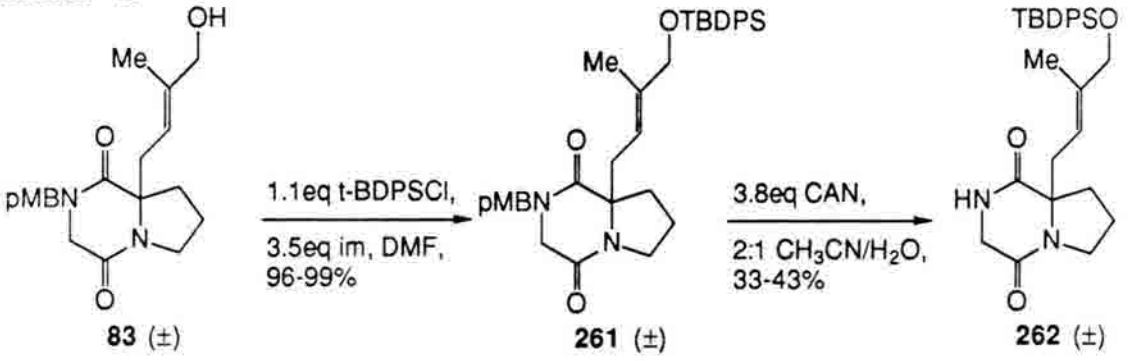
With enal **260** in hand, the total synthesis of (+)-paraherquamide B could now rely on the first eight steps of the (–)-brevianamide synthesis. There was some concern that **260** and the subsequent reduction of the aldehyde of **260** might prove difficult to work with due to the high water solubility of these compounds. It would be ideal if we could formally start with the reduced and protected **252**. Model reactions were done to probe the feasibility of this approach. It seemed likely, that even with the improved ceric ammonium nitrate procedure, the *tert*-butyldimethylsilyl group of **252** would most likely be lost.

Scheme 78


Me
Me
O
pMBN
NBn
O
a) 2eq CAN(0.05M), 2:1 CH3CN/H2O, no reaction
b) 3.8eq CAN(0.33M), 2:1 CH3CN/H2O, 98.6%
HN
258 (±)
259 (±)
3.8eq CAN(0.33M), 2:1 CH3CN/H2O, 86%
256 (±)
257 (±)
CHO
3.8eq CAN(0.33M), 2:1 CH3CN/H2O, quant.
79 (±)
255 (±)
OH
3.8eq CAN(0.33M), 2:1 CH3CN/H2O
83 (±)
260 (±)
82 (±)
260 (±)

We also knew from the model synthesis, that this particular protecting group did not readily survive the demethoxycarbonylation procedure (see Scheme 64). At the same time it would be nice if we could distinguish between the two protected alcohols. This could not be done in the model synthesis when they were both *tert*-butyldimethylsilyl groups. There are only two groups that could possibly fit this bill, including surviving all the later steps: either a *tert*-butyldiphenylsilyl ether or a tetrahydropyran (THP) group. The *tert*-butyldiphenylsilyl group was finally chosen for two reasons. It has been reported that a *tert*-butyldiphenylsilyl group can be selectively removed in the presence of a *tert*-butyldimethylsilyl group.[103] Also, the *tert*-butyldiphenylsilyl group would make all the subsequent compounds uv active (this is no small concern). There was still a fairly large amount of the required allylic alcohol (**83**) available and it was easily protected as the *tert*-butyldiphenylsilyl compound **261**. This material was then exposed with the ceric ammonium nitrate conditions but, the reaction was not as good as we had hoped. The yield of **262** ranged from only 33% to 43% (Scheme 79).

Scheme 79

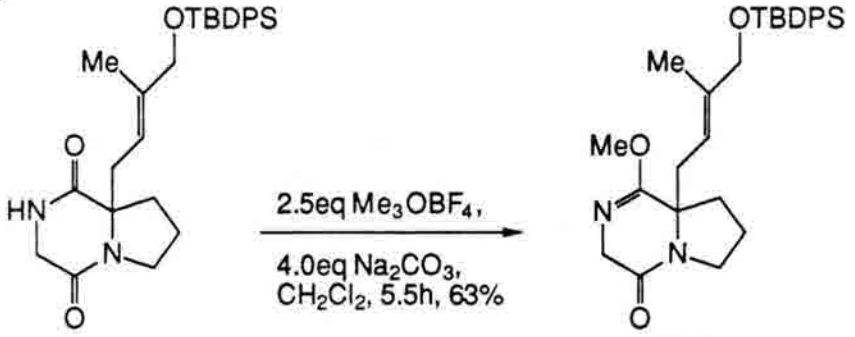


83 (±) **261** (±) **262** (±)

While this reaction would not do from a synthetic standpoint, **262** would prove useful in probing the next series of steps. There still remained the problem of a new protecting group for the free secondary amide. We had planned to block this by converting it to the imino-ether. This particular functionality is not known as a blocking group but it does have the advantage of having a very small steric demand. This was shown to be very important in the S_N2' reaction where, because of the large steric hindrance from the indole and the bulky *para*-methoxybenzyl group the yield of the reaction was quite low (Scheme 60). The

other reason for choosing this group, was to differentiate between the two amides. After the carbocation cyclization, the tertiary amide must be reduced to the amine without affecting the secondary amide. This problem was explored during a synthesis of verruculotoxin by Williams *et al.*.[104] (see Chapter one). Amide **262** was treated with Me_3OBF_4 in dichloromethane with four equivalents of Na_2CO_3 (added to prevent the desilylation of the *tert*-butyldiphenylsilyl group). The yield of **263** was 63%; interestingly, if the Na_2CO_3 was not used the yield of the desired product dropped to a dismal 8% , due to the loss of the silyl group (Scheme 80).

Scheme 80



262 (±) **263** (±)

The next step was to effect the carbomethoxylation of **263**. Compound **263** was treated with 1.5 equivalents of n-butyllithium followed by 1.1 equivalents of methylchloroformate, but no reaction occurred. Various alternative methods were tried to force this reaction, but the desired product was never detected. The most likely explanation for this anomalous result is that the enolate was so stabilized by conjugation with the imidate that the acylating agent would not react, and only starting material was recovered. It is also possible that O-alkylation occurred instead of C-alkylation and the resulting carbonate simple hydrolyzed back to **263** during the aqueous workup. This seems unlikely however, since there was no indication that any reaction occurred (Table 9).

Table 9

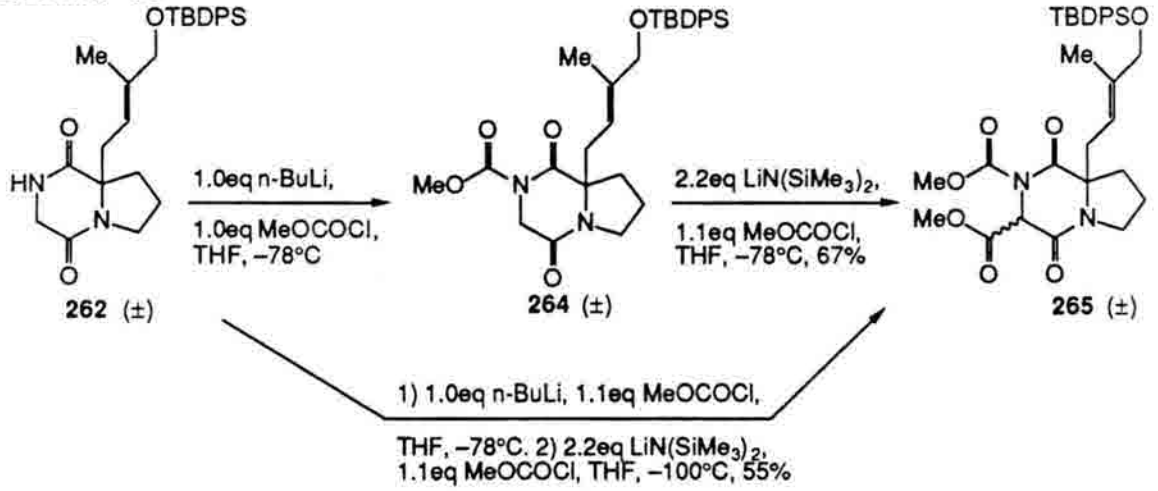
263 (±)

entry	conditions	product(s)
1	1.5eq n-BuLi, 1.1eq MeOCOCl, THF,–78 °C (3.5h) to r.t. (12h)	**263**,no desired product
2	1.2eq n-BuLi, 10eq MeOCOCl, THF, r.t. 28h	**263**,no desired product
3	4.2eq NaH, 1.1eq MeOCOCl, THF, r.t 19h	**263**,no desired product
4	2.3eq NaH, 1.1eq EtOCOCN, 0 °C, DMF, 2h	**263**,no desired product
5	2.3eq NaH, 5.0eq EtOCOCN, 0 °C, DMF,12h	**263**,no desired product

The failure of **263** to react in the prescribed manner was a small problem, so the protection of the lactam as the imino-ether was discarded at this stage in the synthesis. However, it would be needed later for the selective amide reduction. The problem of protecting the lactam still remained, since this would be critical for the Somei condensation with the gramine **220**. The obvious and direct way to protect the lactam moiety of **262** at this time was to convert it to a carbamate while concurrently carbomethoxylating the piperazinedione. Then, after the Somei condensation the two groups could be removed with LiCl/HMPA, and the free lactam would then be reprotected as the imino-ether. We thought that a dianion of this type might prove too unstable; a sequential alkoxycarbonylation would be preferable. The pK_a difference between the two acidic protons (14–16 for the amide vs 20 for the α– methylene) is fairly large so we were confident that by using one equivalent of a strong base the amide would react first. When **262** was treated with 1.1equivalents of sodium hydride in dimethylformamide followed by methylchloroformate at –78 °C there was no reaction. When the base was changed to n-

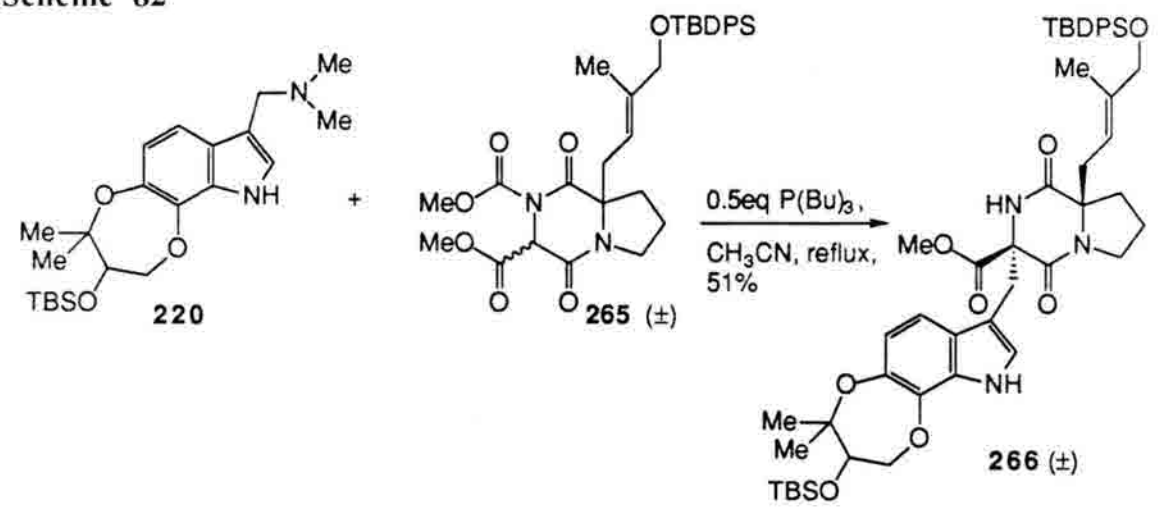
butyllithium and the solvent tetrahydrofuran [105] there was a nearly quantitative conversion (by TLC) of the starting material to a product that was assumed to be the desired N-alkoxycarbonylated compound **244**. At this time an additional amount of the n-BuLi (1.2eq) was syringed into the flask followed a few minutes later by methylchloroformate (1.0eq). The reaction was followed closely by TLC which indicated that the N-alkoxycarbonyl material was slowly decomposing. After the workup there was absolutely no desired product formed, only a small amount of the N-methoxycarbonylated **264** was recovered. It seemed that the choice of n-butyllithium for the second step of this reaction was a poor one. It is known that n-BuLi and other organometallic reagents will attack (and open up) the ring of N-acyl and N-alkoxycarbonyl protected lactams.[105] The recovered material (**264**) was taken and treated with $LiN(SiMe_3)_2$(2.2eq) followed by methyl chloroformate (1.1eq) at –78 °C to provide the desired doubly alkoxycarbonylated compound (**265**) in 67% yield. Various other bases (NaH, LDA) were tried, in order to improve this sequence, but the best results were obtained with n-butyllithium followed by $LiN(SiMe_3)_2$. This reaction was also done as a one pot two-step sequence to give the required product **265** in 55% yield; the second step was done under reverse conditions and at –100 °C (Scheme 81). It is worth mentioning that the workup procedure is critical. If the excess base is not carefully quenched (sat. aqueous NH_4Cl) the product has a tendency to decompose. This is presumably caused by the excess $LiN(SiMe_3)_2$ reacting with water, forming hydroxide that hydrolyzes the sensitive N-alkoxycarbonyl activated lactam.[106] The heightened reactivity of the piperazinedione would play a key role in the stages to come.

Scheme 81



The racemic piperazinedione **265** was reacted with the gramine **220** in refluxing acetonitrile with 0.5eq of tri-butylphosphine for 3 hours. Interestingly the alkylation occurred as expected but, there also was a totally unexpected decarbomethoxylation of the imidic-carbamate leaving the indole **266** in 51% yield (Scheme 82). We suspected that this particular side reaction was caused by dimethylamine that is the main byproduct of this reaction.

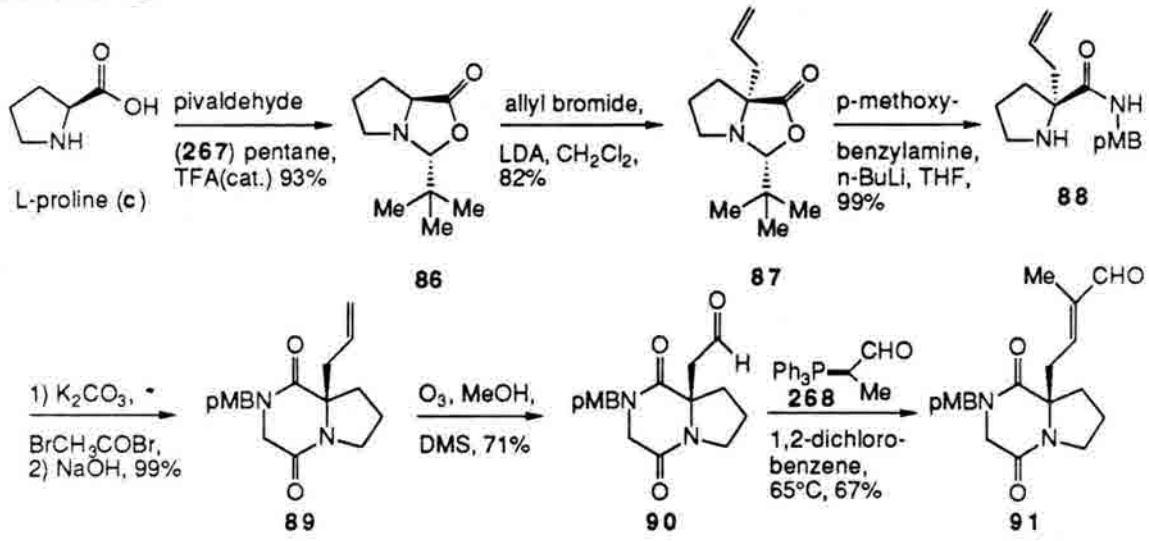
Scheme 82



At this juncture, we were ready to apply this simple model study to the chiral non-racemic case. The condensation of L-proline and pivaldehyde (**267**) [107] was done exactly as reported by Seebach with a slight modification (Scheme 20). The reaction was refluxed for ten days instead of the published six days, because of the larger scale. The unstable

bicyclic product (**86**) was immediately allylated (allyl bromide, LDA, THF) to provide the allylated heterocycle **87** in 76% yield (two steps). By following the procedures of Williams *et al.*, (Scheme 28) this material was aminated with litho-*para*-methoxybenzylamine to supply the amide **88** in 99% yield. This reaction and the next several proved very amenable to large scale work. In a two step one pot reaction, **88** was treated with bromoacetyl bromide yielding the piperazinedione **89** in 39% yield (lit.; 79%, higher yields for this reaction were quite common). This product was ozonolyzed providing **90** in 71% yield (lit. 69%), which in turn was homologated with **268** [108] via a Wittig reaction to give the allylic aldehyde **91** in 67% (lit. 95% small scale) (Scheme 83).

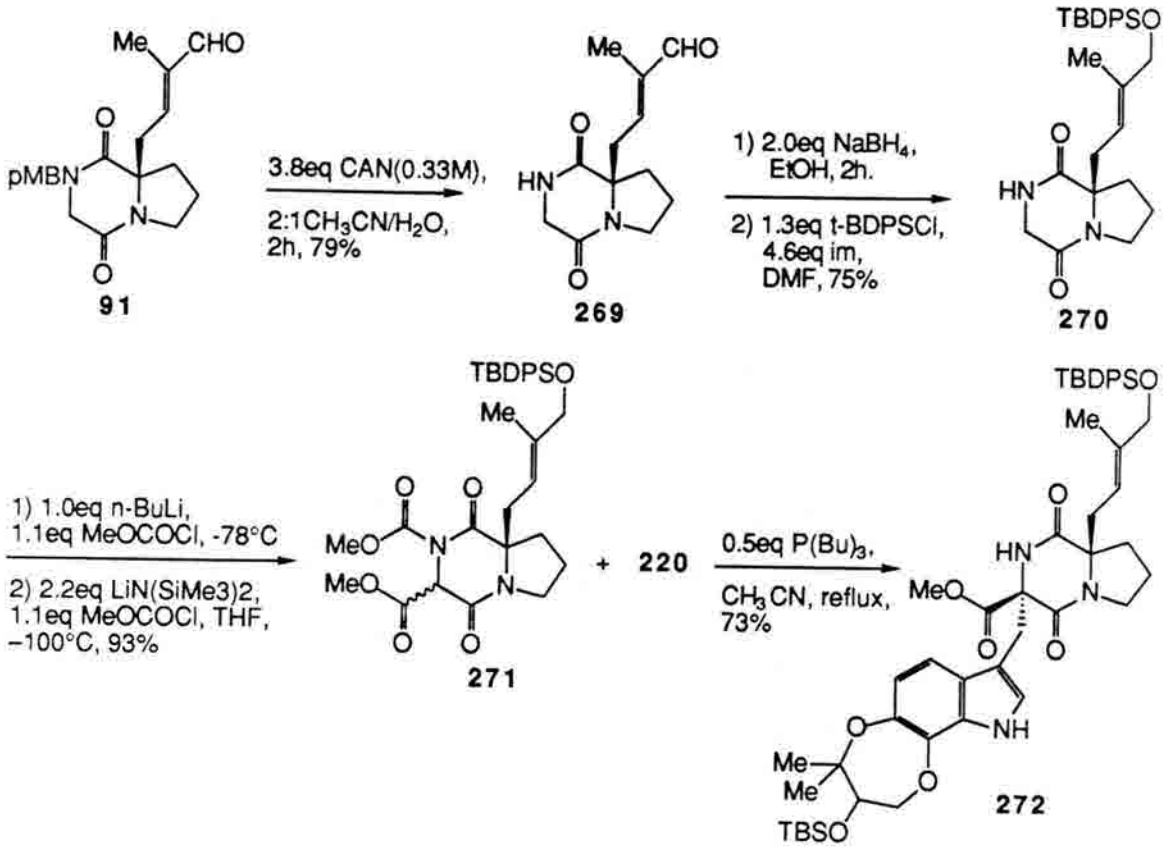
Scheme 83



With large quantities of **91** in hand, we were ready to repeat the work already done on the racemic compounds. Enal **91** was exposed to the ceric ammonium nitrate procedure to provide the secondary amide **269** in 79% yield. This product was reduced with sodium borohydride and protected with t-butyldimethylsilyl chloride in a two-step process to give the silyl ether **270** in 75% yield. This compound was then treated with the two-step one pot alkoxycarbonylation process providing the required substrate **271** in 93% yield. The crude material was a mixture of epimers in a ratio of approx. 4:1 (*syn/anti*). This mixture had a tendency to epimerize during column chromatography, increasing the (*syn/anti*) ratio. The two products were collected together and condensed with the gramine **220** as

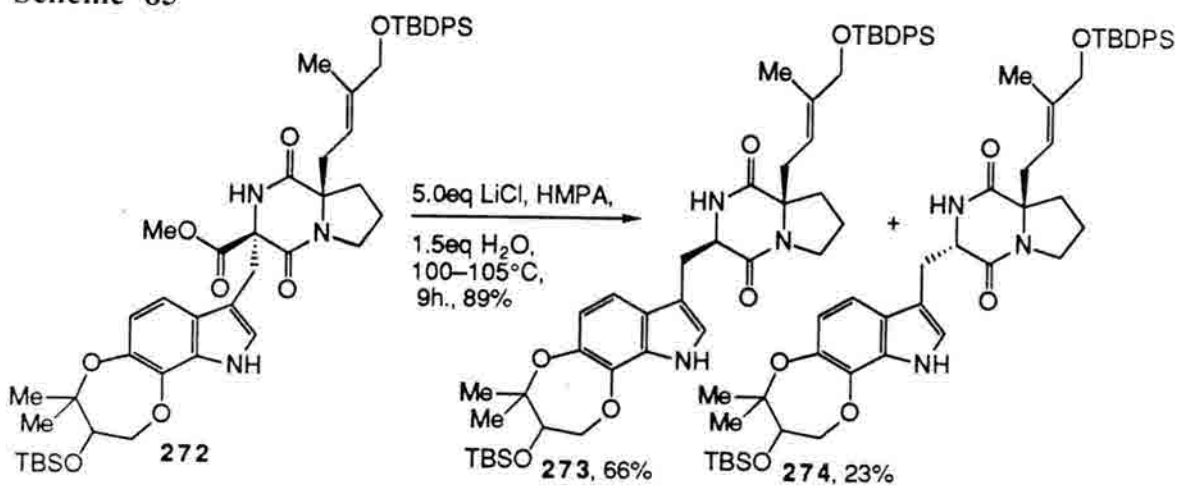
before, providing the indole **272** in 73% yield. All the yields were optimized relative to the racemic series (Scheme 84).

Scheme 84



Compound **272** was treated with lithium chloride in wet hexamethylphosphoramide to effect the decarbomethoxylation; this afforded a 3:1 mixture of **273** *(syn)* and **274** *(anti)* in 89% combined yield (Scheme 85).

Scheme 85

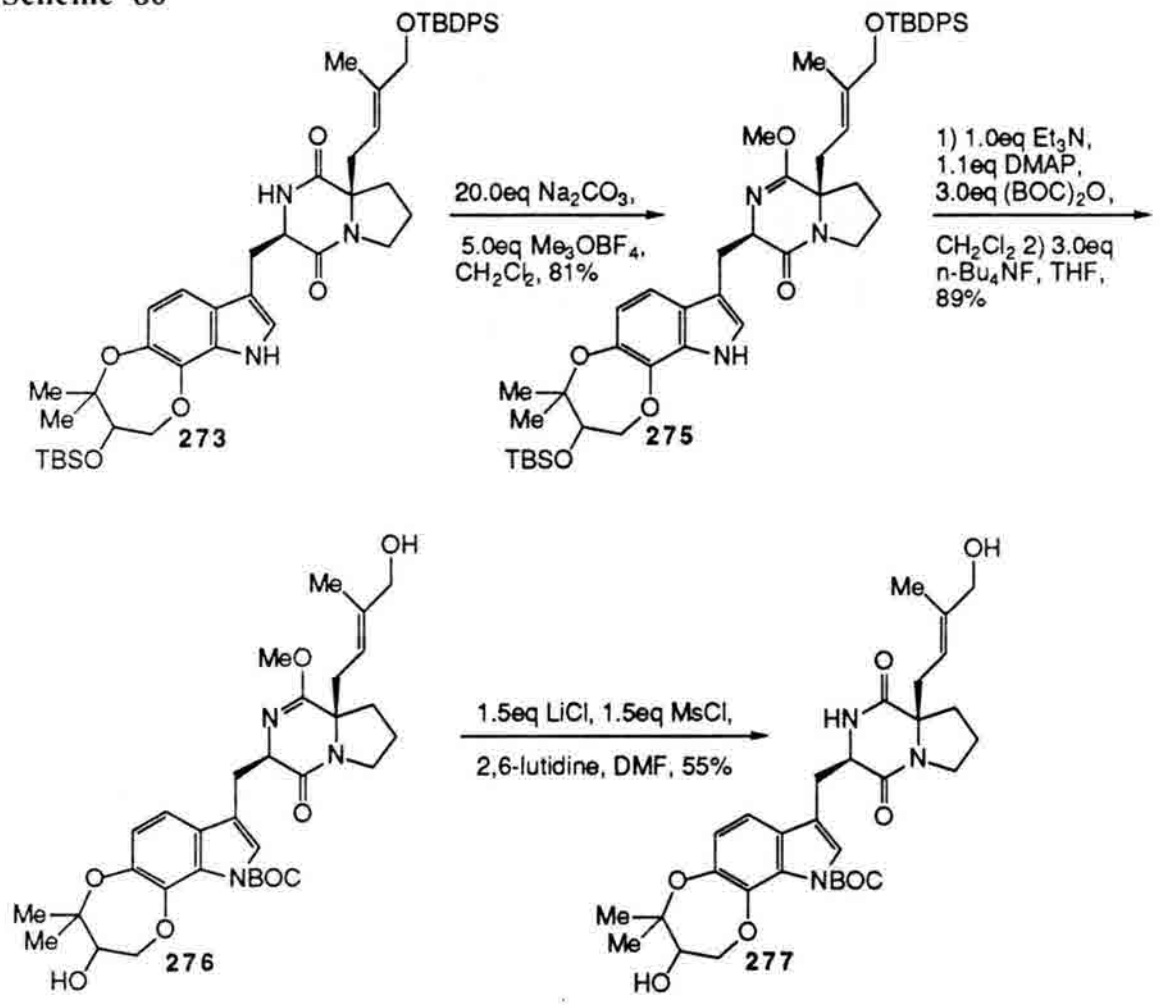


The *syn*-- isomer **273**, was as usual, the most polar and the *anti*- isomer **274** less polar. As expected, there were no problems associated with the loss of the protecting group. The t-butyldiphenylsilyl group stayed in place even at 100 °C for nine hours. In this section and the previous one, there have been wide swings in the relative amounts of the *syn*- and *anti*-diastereomers produced in the demethoxycarbonylation reaction. It has been reported that piperazinedione rings containing proline adopt a boat-like conformation.[109] The boat conformation was implicated as the reason for the production of only one diastereomer *(syn)* during a similar dealkoxycarbonylation of an austamide (**17**) precursor.[13] One face was completely inhibited to protonation of the enolate, because of the large steric hindrance by the tertiary amide nitrogen lone pair. In contrast a similar reaction was done on an alkoxycarbonylated deoxybrevianamide E (**36**) precursor, but with this example, a ratio of 1.5 : 1 (*syn/anti*) was obtained.[26a] Clearly, the reactivity of the paraherquamide precursors is somewhere between these two extremes. This not too surprising from an examination of the three types of compounds. The austamide precursor is the most limited, there are very few degrees of freedom, it is locked into the boat conformation. The deoxybrevianamide E precursor has free rotation of the indolic *exo*-methylene bond, bringing the indole over either face of the piperazinedione. It remains to be seen to what degree the conformation of the piperazinedione deviates from this boat configuration. It is possible that a twist boat or chair type conformation could contribute to this discrepancy. In our case the methine proton is a bulky isopentenyl group that effectively limits the protonation from one side of the molecule. When that face became increasingly blocked the ratio of *syn-/anti* increased from 3:1 for **272** to ≈ 16:1 for **227**.

We were now ready to form the lactim ether; the indole nitrogen should not interfere with this reaction. We did think that the reaction would have to be buffered to prevent the loss of the silyl groups, since this was a problem for the related substrate **262**. The *syn*-isomer **273** (the *anti*-isomer **274** was set aside) was treated with 20 equivalents (optimum) of Na_2CO_3 and five equivalents of Me_3OBF_4 in dichloromethane for four hours. After

chromatography the yield of **275** was 81%. This reaction was actually quite troublesome, and it took a fair amount of tinkering with the conditions to get to the point where it became routine. Even though the next two reactions could be done in a stepwise fashion, it proved most convenient to convert **275** directly to the t-butoxycarbonyl protected diol **276** in a one pot, two step sequence. Diol **276** was then subjected to the chlorination procedure successfully used in the conversion of diol **231** to the allylic chloride **232**. Unfortunately, under these conditions, **276** was converted to the lactam **277** in 55% yield. Apparently no chlorination took place, and the free chloride nucleophilically displaced the lactim ether (Scheme 86).

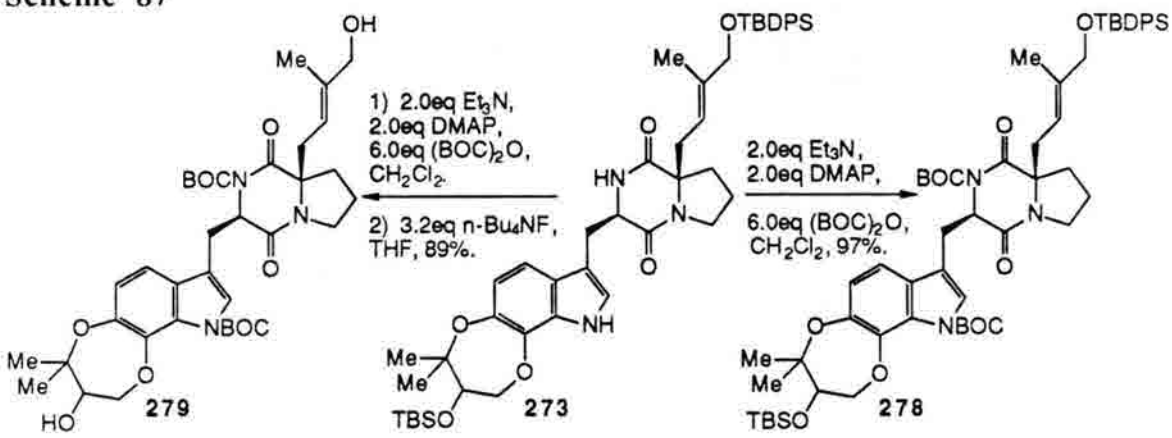
Scheme 86



We therefore chose to work on a slightly different approach. The conversion of **275** to the diol **276** was facile, so we decided to use this procedure to protect the amide

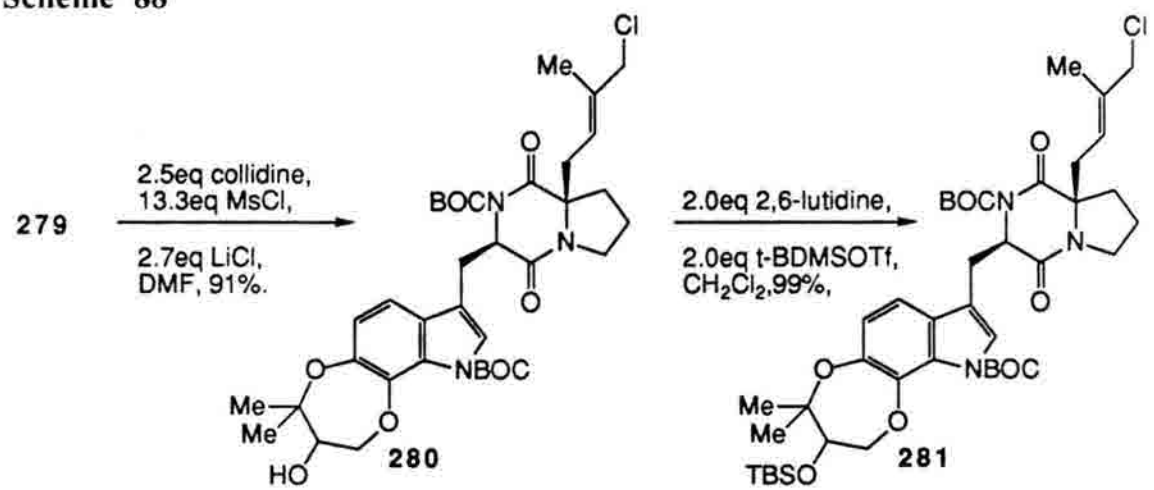
and the indole together. This would allow the cleavage of the silyl groups in the same pot. The lactam **273** was treated with triethylamine and 4-dimethylaminopyridine followed by di-*tert*-butyl dicarbonate; the reaction was complete after 8.5 hours providing **278** in 97% yield. It is worth mentioning that the reaction rate of the two different reaction sites was so close that it didn't seem likely that the amide could be selectively protected in the presence of the indole or vice versa. An attempt was made to selectively desilylate the allylic alcohol of **278** according to the known procedure (NAH, HMPA),[103] but **278** suffered only slow decomposition under these conditions. The t-butoxycarbonyl protected compound **278** could be nonselectively desilylated (n-Bu_4NF), but again it proved more convenient to do the conversion in one pot providing the diol **279** in 89% yield (Scheme 87).

Scheme 87



There was no problem in converting diol **279** to the allylic chloride. Reaction of **279** (LiCl, MsCl, collidine, DMF) supplied the chloride **280**, which was then carefully reprotected with t-BDMSOTf and 2,6-lutidine. To prevent the transesterification reaction [90] the reagents were added portion wise; by this method **281** was easily obtained (Scheme 88).

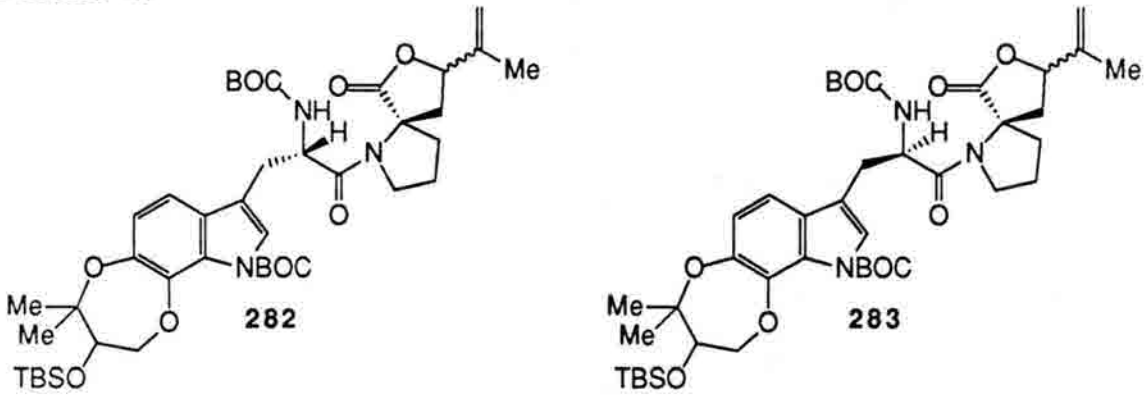
Scheme 88



Many S_N2' reactions were tried on substrate **281**, and depending on the conditions, the reaction would produce many or no products. The allylic chloride **281** was first allowed to reflux with 20 equivalents of sodium hydride in benzene for approx. 22 hours. The TLC showed total decomposition. The reaction was repeated with only 10 equivalents of sodium hydride, in benzene and 4Å molecular sieves. It was allowed to stir overnight at room temperature. Judging by TLC, there was no reaction. The mixture was then refluxed for four hours and five products were isolated. The two least polar compounds **282** (R_f = 0.42) and **283** (R_f = 0.38) had very interesting nmr spectra They were apparently diastereomers of each other, and both had a doublet centered at ≈5ppm indicative of an olefinic *exo*-methylene. This reaction was repeated but with the temperature controlled (40–43 °C for 48 hours). Five products were again isolated; three were totally new but the other two corresponded to **282** and **283**. This reaction was also done in tetrahydrofuran instead of benzene, but three entirely new products were isolated, but none of which were recognizable. The base was changed to $NaN(SiMe_3)_2$ and stirred in toluene for 2 days at low temperature (–78° to –23 °C) but, only decomposition products were found. This same reaction was done with sodium hydride in dimethylformamide at room temperature, resulting in a large number of unidentifiable products. In an effort to increase the reactivity, the allylic chloride in **281** was converted to an iodide (5.0eq NaI, acetone) and immediately refluxed with sodium hydride in benzene. This seemed to make

little difference in the product distribution. This was also tried with $KN(SiMe_3)_2$ instead of sodium hydride and tetrahydrofuran instead of benzene giving small amounts of **282** and **283**. The similarity of all these reactions was the appearance of the unknown products **282** and **283** although in all cases the yield was extremely poor. An intensive effort at the structural elucidation of these mysterious products was undertaken; ^1H NMR($CDCl_3$) Homodecoupling, ^1H NMR(D-6 acetone) Homodecoupling, ^{13}C NMR, DEPT 90, 135, HETCOR, IR, MS, led us to conclude that the two products were the spirolactones (Scheme 89), (Figures 5, 6).

Scheme 89



The stereochemistry α– to the secondary amide remains in question. The assignments are made strictly from supposition obtained from their Rf values, and compared to the diastereomers **273** and **274**. It seems likely that the failure of **281** to cyclize in the desired fashion can be attributed to the increased steric bulk of the t-butoxycarbonyl of the amide. The reason for the formation of the two spiro compounds must be due to the increased reactivity of the amide. The t-butoxycarbonyl group has a strong electron withdrawing influence upon the piperazinedione amide, in effect weakening the amide bond to the point where it is susceptible to nucleophilic ring opening.[105,106] Similar reactivity was noted in the formation of piperazinedione **265**. Apparently, any moisture in the reaction mixture reacted with the sodium hydride forming hydroxide that then hydrolyzed the reactive amide bond. The resulting carboxylic acid cyclized in an S_N2' reaction furnishing the spiro lactones.

Figure 5, 282

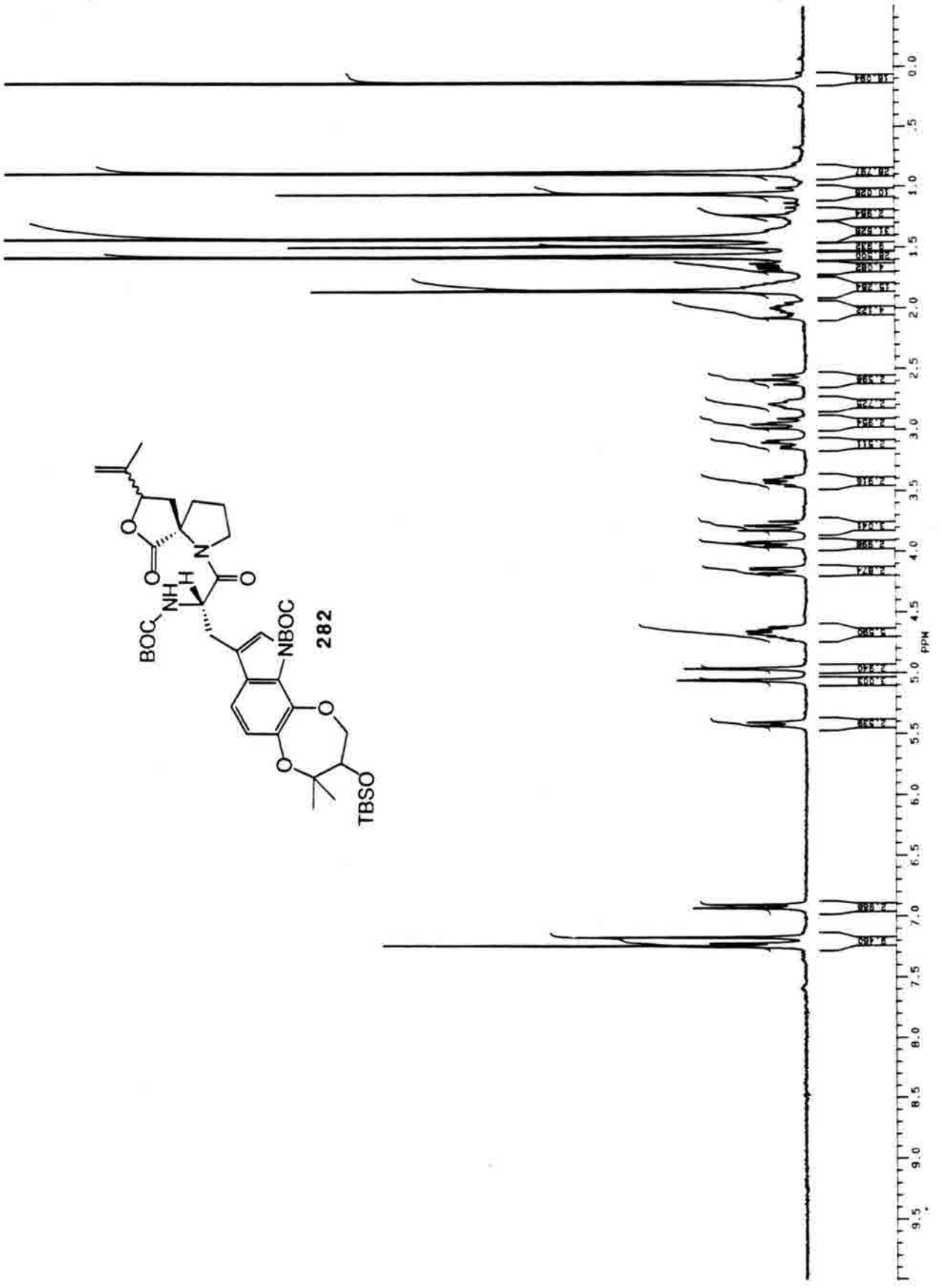


Figure 6a, 283

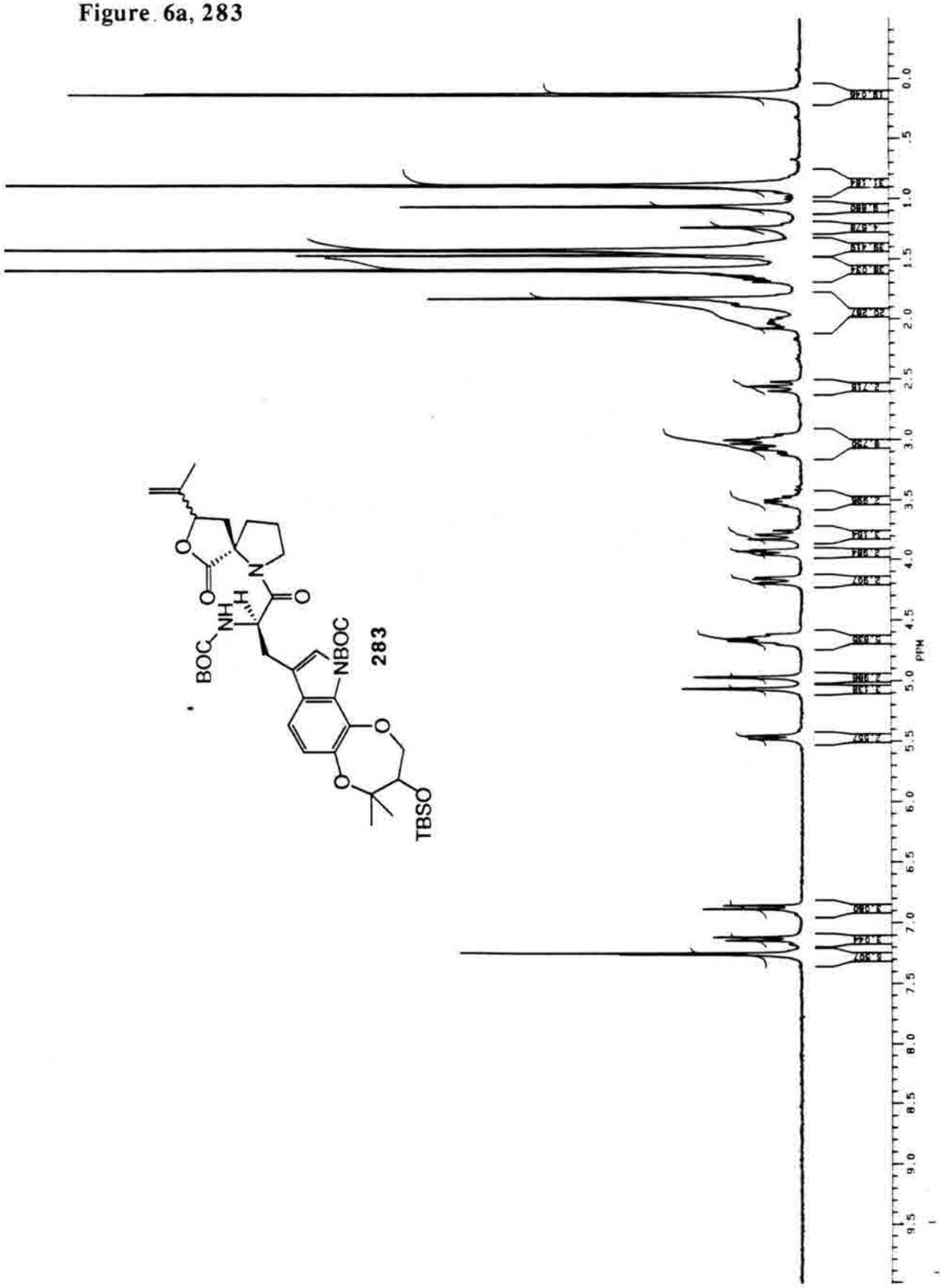
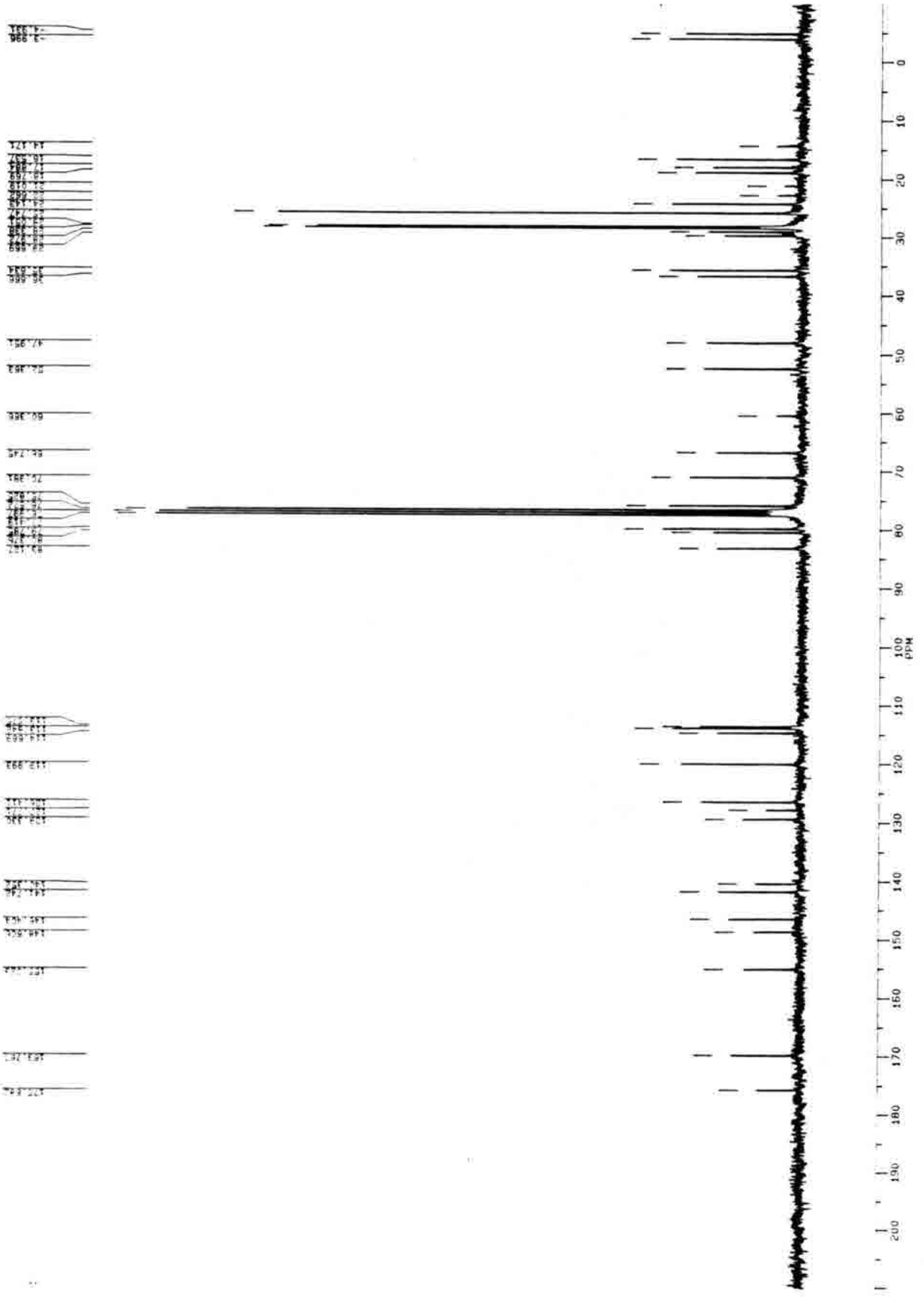
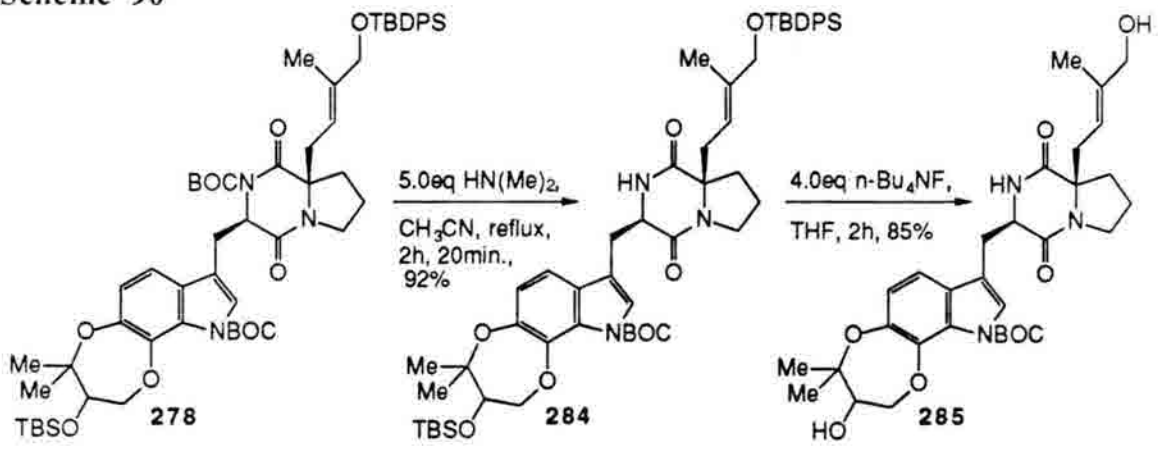


Figure 6b, 283



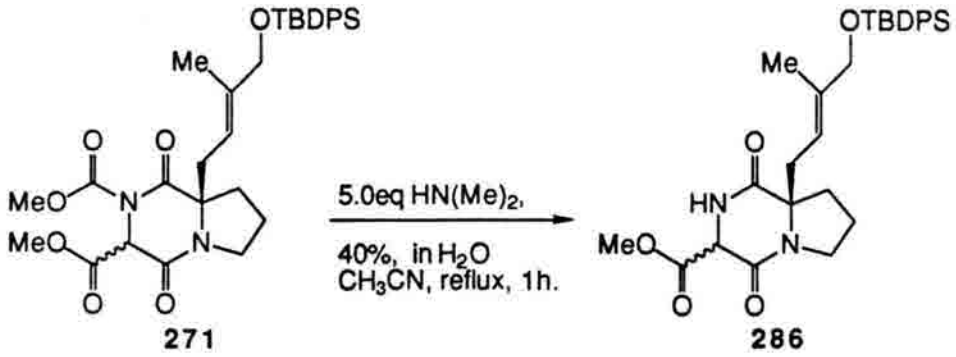
This mechanism is reasonable considering that the best yields were obtained when the possibility of water entering into the reaction mixture was the greatest. This also reinforced our earlier supposition about the problem with a bulky blocking group for the amide. This thought was uppermost in our mind when we decided to explore alternative groups for this lactam. By replacing it with something smaller and less electron withdrawing, the S_N2' reaction might prove possible. As was mentioned before, we thought that the reason for the loss of the lactam methoxycarbonyl group in the alkylation of **271** was due to the dimethylamine byproduct. Perhaps this was a general reaction that could be used to deprotect the lactam t-butoxycarbonyl group of **278**. This would give us the unlimited possibility of finding a suitable group to put in its place; additionally, this could also help in fine tuning the selectivity of the S_N2' reaction. After refluxing a solution of **278** and dimethylamine in acetonitrile for two hours and twenty minutes, the reaction lavished upon us the predicted product **284** in 92% yield. We decided to see if it might be possible to do the S_N2' reaction on the unprotected lactam. We desilylated **284** with a controlled amount of tetra-n-butylammonium fluoride granting the diol **285** (Scheme 90).

Scheme 90



The generality of the alkoxycarbonyl deprotection was looked at more closely when **271** was refluxed in acetonitrile and five equivalents of dimethylamine for one hour. The product was as expected, the demethoxycarbonylated lactam **286** (Scheme 91).

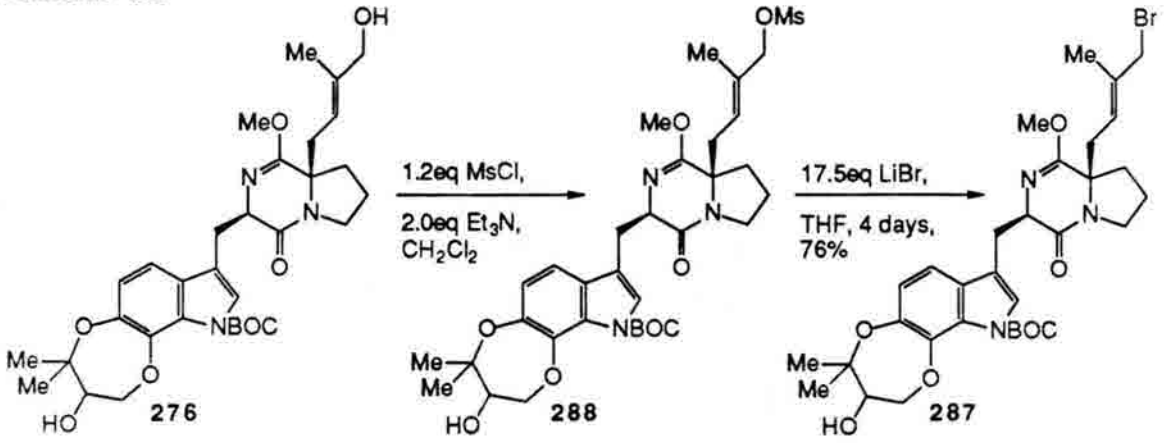
Scheme 91



This is a remarkable result especially in light of a report that *tert*-butoxycarbonyl protected amides are cleaved to the *tert*-butoxycarbonyl protected amine with DEAEA (diethylamine ethylamine) in acetonitrile at room temperature.[110] However, the substrates tested in that report were all open chain amides; and lactams were never discussed. Grehn *et al.*.[110] mentioned that these same t-butoxycarbonyl protected amides were cleaved with basic alcoholysis, analogous to our unexpected production of the spiro compounds **282** and **283**. Interestingly, other amines were found to effect amidolysis, but dimethylamine was never mentioned. An attempt was made to convert the diol **285** to the allylic chloride using the previously described conditions. The reaction was fairly clean but the product proved to be the corresponding mesylate. We knew that a mesylate was too reactive to withstand the t-BDMSOTf step, so this compound was set aside. In fact the entire approach starting from the lactam **284** was discarded at this time due to the final success of the imino-ether route. After the initial failure of the Meyers procedure to effect chlorination of the lactim ether **276**, we turned to alternative approaches to perform this key transformation. When **276** was treated with a stirred solution of TsCl (1.2eq) and DMAP (2.0eq) in dichloromethane for four days,[111] the only product isolated was the allylic tosylate, together with some unreacted starting material. There was no trace of the desired chloride (presumed to form *in situ* from the tosylate). While tosylates are excellent leaving groups, this allylic tosylate was deemed too reactive to withstand the conditions needed to protect the secondary alcohol. In the brevianamide work, an allylic tosylate did not to cyclize under an attempted S_N2' reaction. A similar reaction was tried on **276** with

methanesulfonyl chloride in methylene chloride and triethylamine. After one day, a product assumed to be the mesylate was treated with a large excess of lithium bromide in tetrahydrofuran. Within four days the reaction was complete furnishing the desired allylic bromide **287** in 76% yield (Scheme 92).

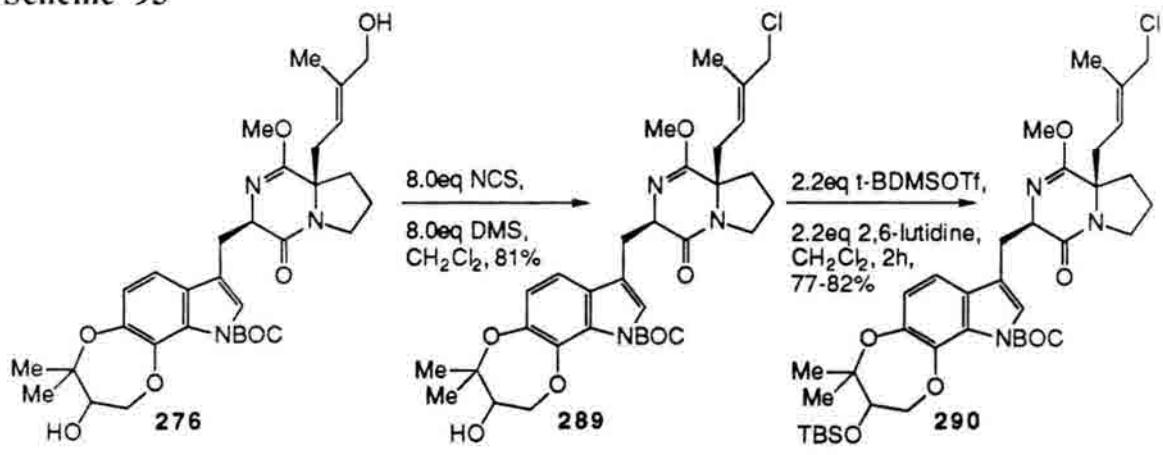
Scheme 92



This product was taken on to the protection step involving t-BDMSOTf. Unfortunately, the two products isolated were the *tert*-butyldimethylsilyl protected free indole and a compound that looked like a diol. Apparently, the bromide was too reactive for these conditions. The previous reaction (MsCl, Et_3N, CH_2Cl_2) was repeated but this time two products were found, the mesylate (**288**) and also the desired allylic chloride (**289**) in very low yield. The procedure of Meyers (MsCl, LiCl, collidine, DMF) was tried again, but this time a less ionizing solvent was used. Previously, DMF was deemed to be the cause for the loss of the lactim ether; employment of dichloromethane was expected to avoid this problem. However, the only product found was the mesylate **288**. An attempt was made to protect (t-BDMSOTf, 2,6-lutidine, CH_2Cl_2) the secondary alcohol of **288**, but there was extensive decomposition of this material. This mesylate **288** was also treated with a solution of lithium chloride in tetrahydrofuran with the aim of displacing the mesylate, but there was absolutely no reaction after three days. The same reaction was attempted in acetone with similar results. We were now trapped in a corner: conditions needed to convert the mesylate to the chloride caused the loss of the lactim ether, but a more

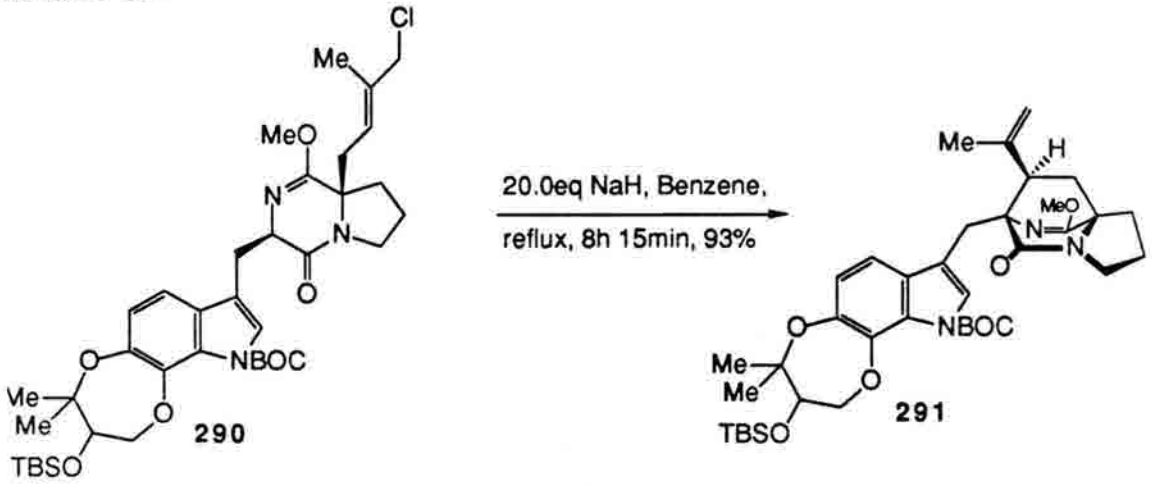
reactive nucleophile (bromide) resulted in a product that is too reactive for subsequent steps. The lack of reactivity of the secondary alcohol during this work was intriguing. Perhaps, a non-selective method to convert alcohols to chlorides would be useful. Diol **276** was treated with solution of triphenylphosphine and carbon tetrachloride. After one hour there was no reaction, the flask was then heated to 65 °C; unfortunately after the workup there were at least three products formed. This result led us to discard the mild method using hexachloroacetone and triphenylphosphine.[112] This whole problem was finally solved by embracing the procedure of Corey,[113] essentially a modified Corey–Kim oxidation but without the base. When **276** was added to a mixture of N-chlorosuccinamide and dimethylsulfide at 0 °C–(–23 °C), the chloride **289** was slowly formed in 81% yield; however, this reaction was somewhat problematic. It was extremely sluggish. On a large scale it had to be stirred all day at –23 °C and then placed in the freezer (approx.–35 °C) and stirred for an additional period. If the reaction mixture was placed in the freezer one more night total decomposition would result. Chloride **289** was reprotected with t-BDMSOTf to provide **290** in 77–82% (Scheme 93).

Scheme 93



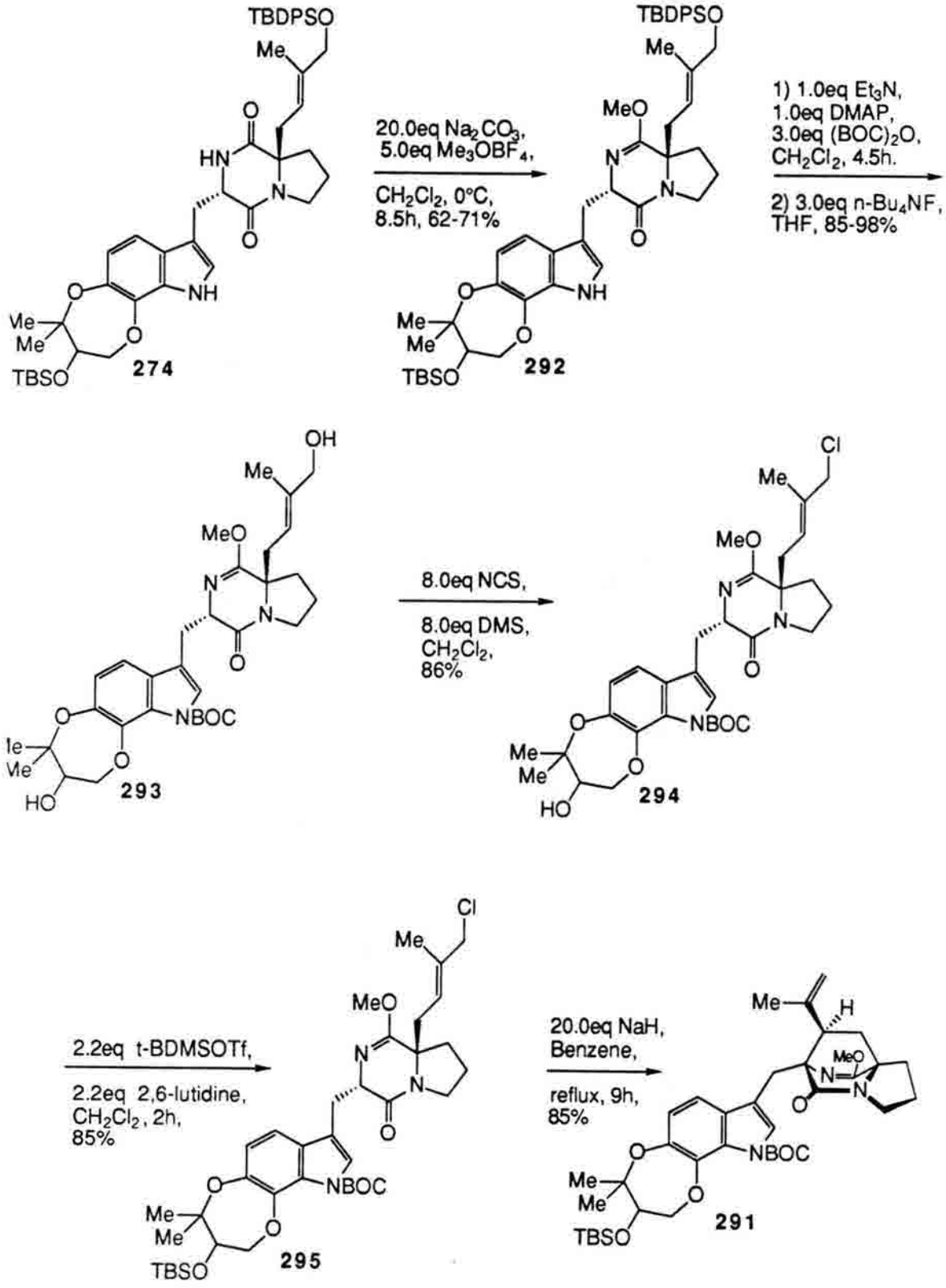
The stage was now set to effect the S_N2' reaction. Chloride **290** was refluxed in benzene with twenty equivalents of sodium hydride bestowing the desired product **291** in 93% yield (Scheme 94).

Scheme 94



The judicious use of our resources called for us to repeat this last series of reaction on the *anti*-isomer **274**. Treatment of **274** with Me_3OBF_4 in Na_2CO_3 in dichloromethane provided the lactim ether **292** in 62–71% yield. The yields for this reaction were consistently lower than the reaction of the *syn*-isomer **273**; it also took about twice as long to go to completion. This was not too surprising, considering that **273** is more congested than **274**. The *syn*-isomer has one face entirely open while the *anti*-isomer is relatively hindered on both sides of the molecule. Lactim ether **292** was subsequently treated with the indole protection and desilylation procedures already worked out for the *syn*-case. This two step-one pot process gave the diol **293** in 85–98% yield. This product was then treated with n-chlorosuccinimide (NCS) and dimethylsulfide (DMS) to afford the chloride **294** in 86% yield. This reaction proved much easier than the corresponding *syn*-substrate; again this was probably a consequence of steric effects. In the *anti*-case there is much less spatial interaction around the alcohol; the NCS–DMS complex therefore has more room for attack by the alcohol. In the *syn*- case there is not a great deal of room for approach since the indole takes up a great deal of the space. For similar reasons the resilylation(t-BDMSOTf) of **294** was slightly better (providing **295** in 85–88% yield) than the same reaction of **290.** The *anti*-chloride **295** was then refluxed in benzene with the required amount of sodium hydride to yield the same product **291** as before (Scheme 95).

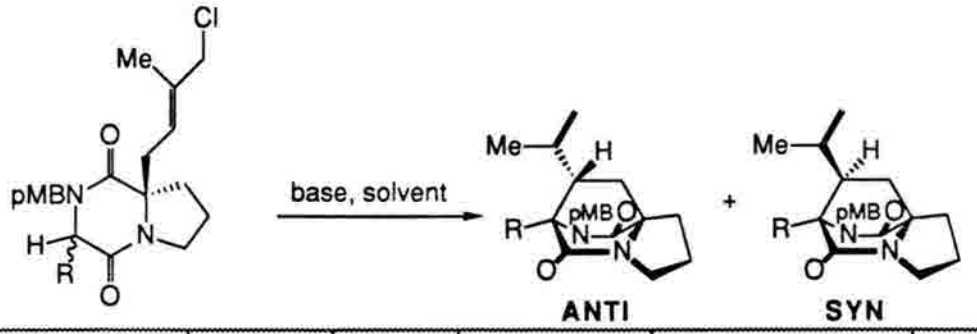
Scheme 95

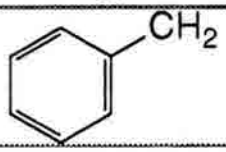
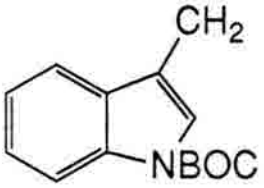

TBDPSO
Me
HN
NH
TBSO
274
20.0eq Na2CO3,
5.0eq Me3OBF4,
CH2Cl2, 0°C,
8.5h, 62-71%
MeO
292
1) 1.0eq Et3N,
1.0eq DMAP,
3.0eq (BOC)2O,
CH2Cl2, 4.5h.
2) 3.0eq n-Bu4NF,
THF, 85-98%
OH
NBOC
HO
293
8.0eq NCS,
8.0eq DMS,
CH2Cl2,
86%
Cl
294
2.2eq t-BDMSOTf,
2.2eq 2,6-lutidine,
CH2Cl2, 2h,
85%
295
20.0eq NaH,
Benzene,
reflux, 9h,
85%
291

The yields of **291** from both routes were very high and there was absolutely no undesired ("*exo*-") diastereomer ever formed. This reaction was performed numerous times and all attempts to find this missing diastereomer failed. Only the *endo*-product was found. There were a few other by-products isolated, but the only one that was recognizable was the S_N2' product that had lost the *tert*-butoxycarbonyl protecting group. Fortunately, a macrocyclic product like **233** was never identified. The S_N2' reaction is quite interesting, and warrants some elaboration. In the synthesis of (–)-brevianamide B (**38**) Williams *et al.* [24c,d] found that in polar aprotic solvents, the major product was usually the *exo- (anti)* product, while in a nonpolar solvent (benzene) under heterogeneous conditions the *endo- (syn)* product predominated. Their work is summarized below (Table 10). This data was interpreted by Williams as follows. In a good cation-solvating solvent (polar aprotic) such as dimethylformamide, the sodium cation is trapped in a solvent cage in the vicinity of the enolate. This solvent cage because of its bulk, prevents the allylic chloride moiety from approaching the enolate in an *endo*-manner. Thus, the transition state leading to the *syn*-product is blocked, and the majority product *(anti)* stems from the less sterically hindered *exo*- mode. In the case of a poor cation-solvating solvent, such as benzene, the enolate associates tightly to its counterion. It is this association that forces the allylic chloride moiety to fold over the enolate so that the developing chloride anion forms a tight contact ion pair with sodium cation. The *exo*- mode should have considerably lower energy in the transition state relative to the *endo*-mode; thus, the *syn*-product would predominate. In direct support of this hypothesis, Williams found that if a crown ether was used in the reaction, increasing the bulk of the solvent shell, a much improved ratio of *anti*- to *syn*- diastereomers would result. This even occurred when the reaction was done in benzene. This explanation is in need of elaboration. It is generally accepted that S_N2' reactions favor a *syn*-orientation.[114] This is for two reasons. First, the incoming nucleophile displaces the π electrons, putting them in the proper orientation for backside attack of the C_α-Cl bond. Second, a *syn*-approach has the advantage that the developing

leaving group can be pulled off at the same time that the incoming nucleophile is "pushing", resulting in a cyclic (closed) transition state.

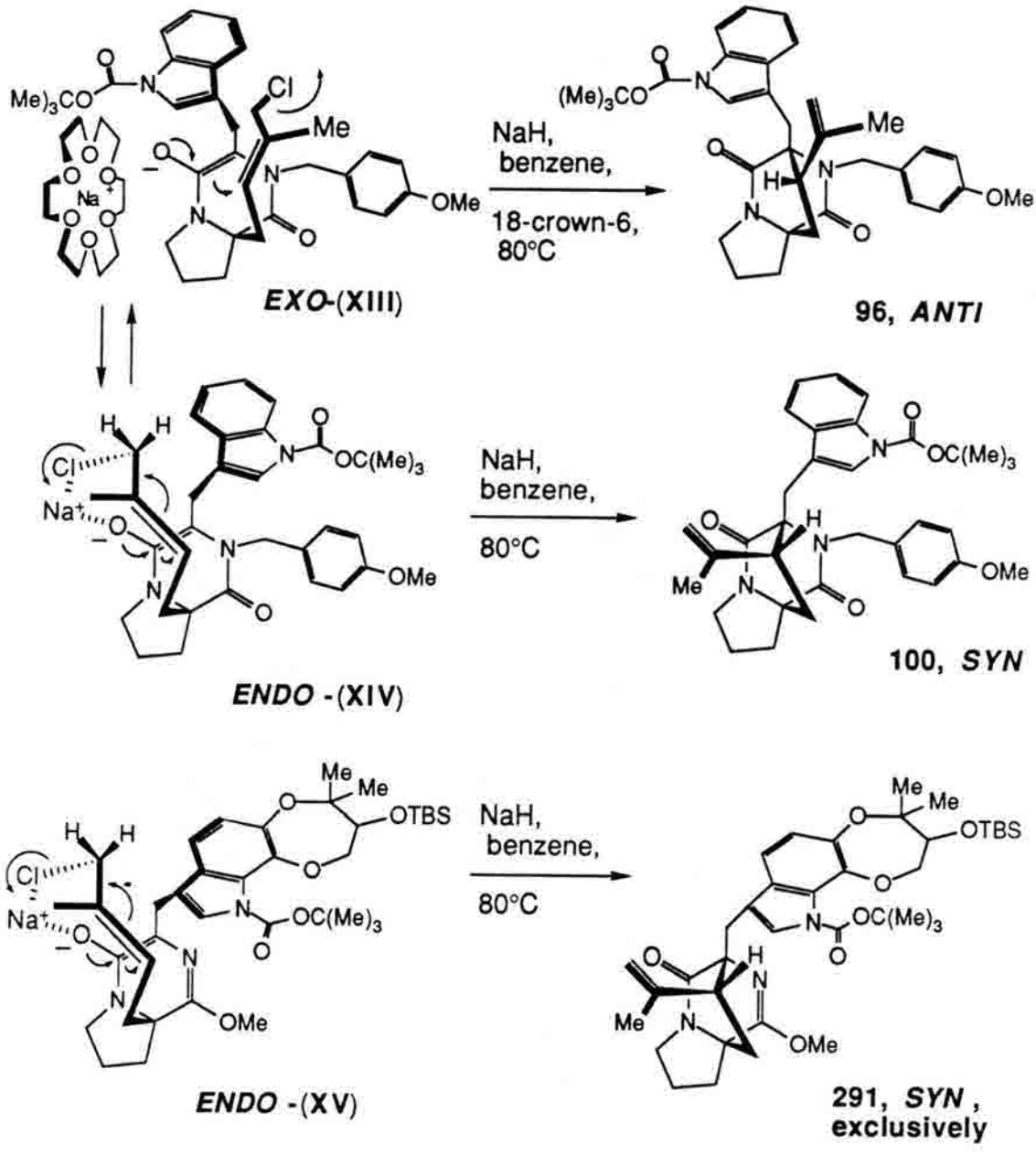
Table 10



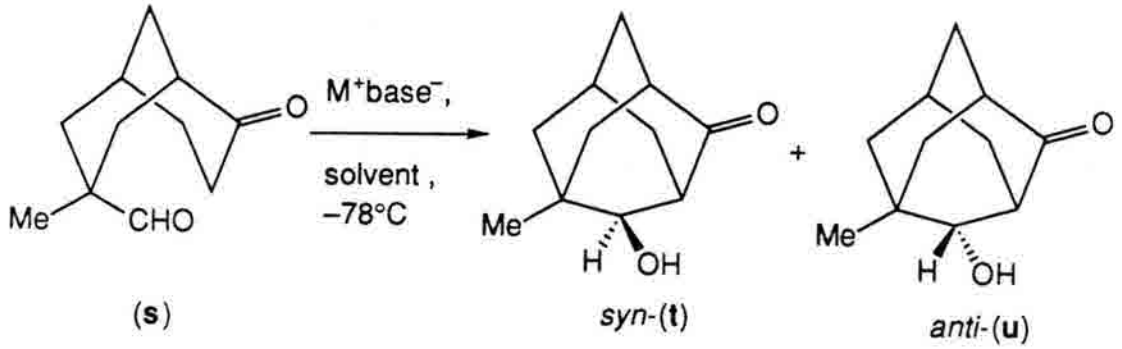
substrate(R)	solvent	Temp.	base	ratio(*anti/syn*)	yield
H	DMF	25 °C	NaH	10:1	60%
H	benzene	80 °C	NaH	≈0:1	10%
	DMF	25 °C	NaH	2:3	65%
	benzene	80 °C	NaH	≈0:1	20%
	DMF	25 °C	NaH	2:1	63%
	benzene	80 °C	NaH	3:97	82%
	benzene	80 °C	NaH/18-Cr-6	3.9:1	56%
	benzene	80 °C	KH/18-Cr-6	1.1:1	38%
	benzene	80 °C	NaH/15-Cr-5	1.42:1	40%
	benzene	25 °C	NaH/18-Cr-6	6:1	14%
	THF	67 °C	NaH/18-Cr-6	4.9:1	64%

The idea that the stereochemical outcome of an intramolecular enolate alkylation is determined by a chelation in the transition state was recently demonstrated quite effectively by Denmark and coworkers.[115] They were exploring the stereoselectivities of special intramolecular aldol condensations. They found a marked preference for a closed transition state (coordination of the cationic counterion to an enolate and the developing alcohol) resulting in a *syn*-product. The selectivity observed between the closed transition state and the open

Scheme 96



Denmark's intramolecular aldol condensations

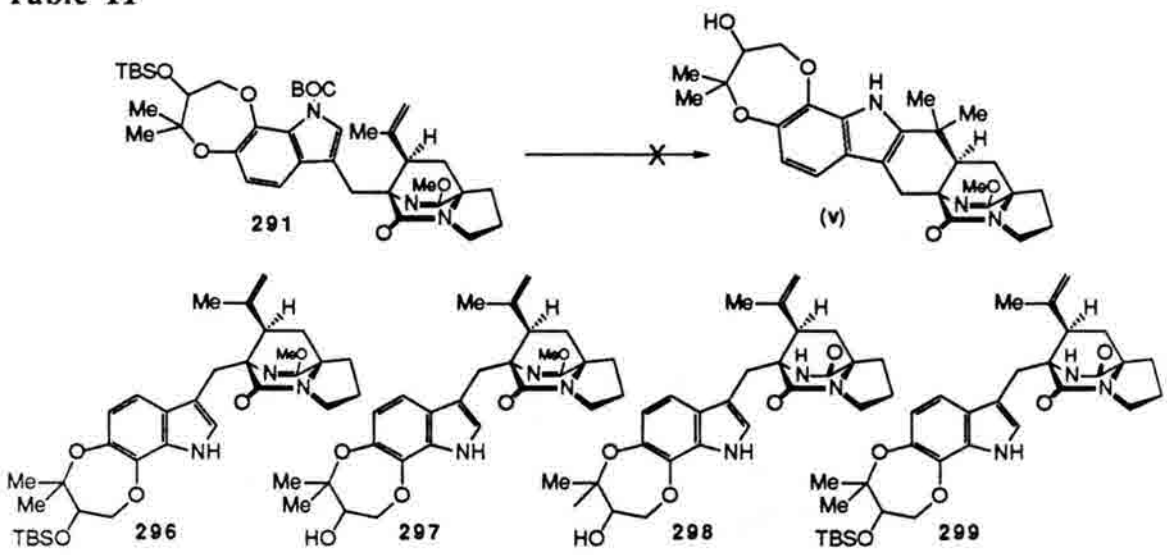


(**s**) *syn*-(**t**) *anti*-(**u**)

one giving the *anti*-product could be obviated by changing the reaction conditions. For example, the highest ratio (89:11) of *syn/anti* was obtained in toluene and the lowest ratio (2:98) of *syn-/anti* was obtained with a crown ether (see Scheme 96). Their results parallel our results with the intramolecular S_N2' reaction. Apparently, the *para*-methoxybenzyl protecting group plays no real role in determining the selectivity for this reaction. It appears only to influence the overall reaction rate. Recall that in the model system (conversion of **234** to **235**) the yield was poor (11%) and the reaction took 13 days. In contrast the yield was quite high and the rate was greatly increased when the lactim ether protecting group was used (conversion of **290** and **295** to **291**),(Scheme 96).

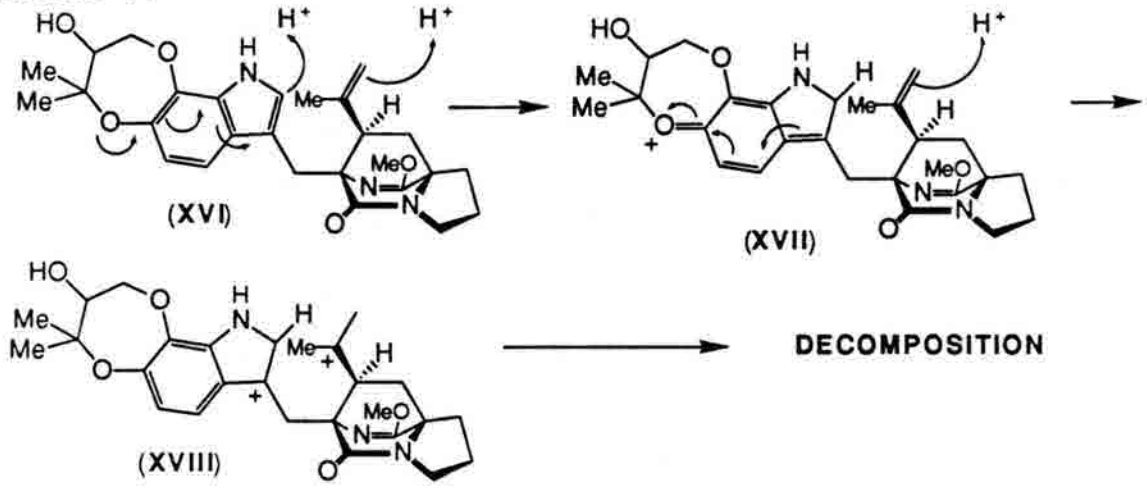
At this stage we were ready to perform the cationic cyclization, exactly as in the brevianamide synthesis. We had assumed that the silyl ether and the *tert*-butoxycarbonyl protecting groups would both be cleaved under these conditions, and it was highly likely that the lactim ether would be cleaved as well. The method employed (strong mineral acids) is well precedented to effect this type of transformation.[116] To our great disappointment, no cyclized product of any kind was ever found. The conditions were varied using different acids and temperatures, but the only recognizable products were those stemming from the loss of protecting groups. If these reactions were allowed to stir longer, only decomposition products would be formed (Table 11). This was a major setback. Mechanistically, the problem appears to be the increased basicities of the 2-position of the indole due to the stabilizing influence of the oxygen atom at the 6-phenolic position. Protonation at the 2-position would prevent the cyclization from occurring. This must be at least kinetically competitive with olefin protonation (Scheme 97).

Table 11



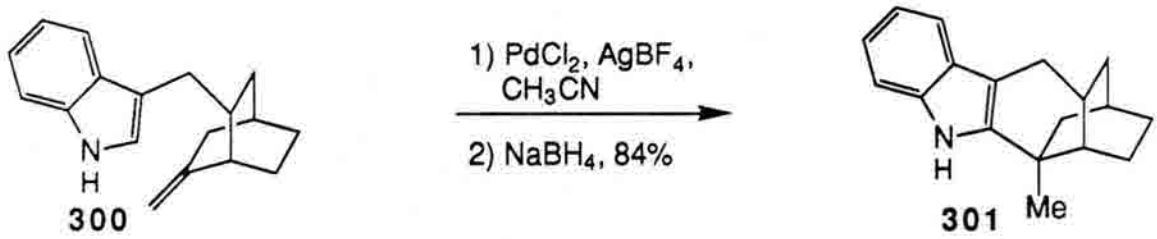
entry	conditions	product(s)
1	$HCl_{(conc.)}$/dioxane(9–16 °C) 2days	3 products(unidentifiable)
2	$HCl_{(conc.)}$/dioxane(–35)–0 °C 2days	3 products(unidentifiable)
3	$HCl_{(g)}$/dioxane(9–16 °C) 6h	no identifiable product
4	$HCl_{(g)}$/dioxane(9–16 °C) 0.5h	**297**
5	$HCl_{(g)}$/dioxane(0–2 °C) 2.5h	**298**, and 3 unknown products
6	HCl/THF,dioxane,15 °C 19h.	5 products(unidentifiable)
7	TFA, trifluoroethanol, –40 °C,3days	**299**
8	TFA, trifluoroethanol, –78 °C,3days	**296**
9[117]	3.0eq TMSOTf,CH_2Cl_2, –78 °C,8h	**296, 297**
10	3.5eq TMSOTf,CH_2Cl_2, 0 °C,22h	**298**
11	$BF_3{\cdot}OEt_2$, HF, dioxane 15 °C 24h	**298**

Scheme 97



At this point, the outlook was bleak, and there seemed no way around this problem. Luckily we fortuitously stumbled across a fairly obscure paper.[122] In this publication, Trost *et al.* used $PdCl_2$ and $AgBF_4$ to effect the cyclization of various isoquinuclidine model compounds. Interestingly, the highest yield came from the *exo*-methylene substrate **300** (Scheme 98).

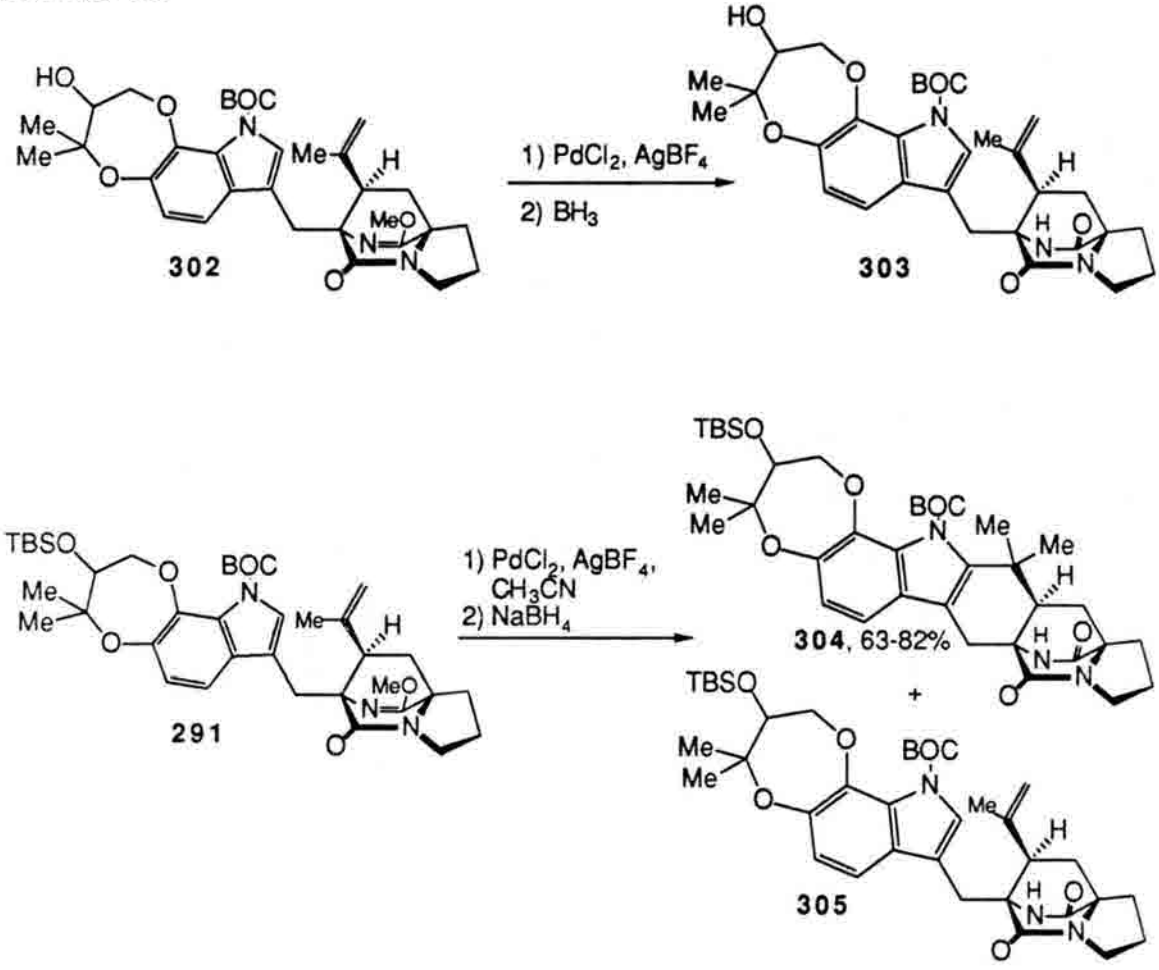
Scheme 98



This was exactly what we were looking for. Our initial experiments were performed with the desilylated compound **302**, easily prepared from **291**. We thought that the silyl group might cause problems in the presence of the BF_4^- anion, because we encountered this problem before with Me_3OBF_4. Unfortunately, the reaction of **302** using the Trost conditions primarily gave back the free lactam **243**, even though there was a hint that some cyclized products were being formed. Perhaps the free alcohol was interfering in some way, preventing the cyclization from occurring. When the totally protected S_N2'

product **291** was exposed to these same conditions, it cyclized quite readily, awarding us the heptacycle **304** in 63–82% yield. The main byproduct was the uncyclized free lactam **305** (Scheme 99).

Scheme 99



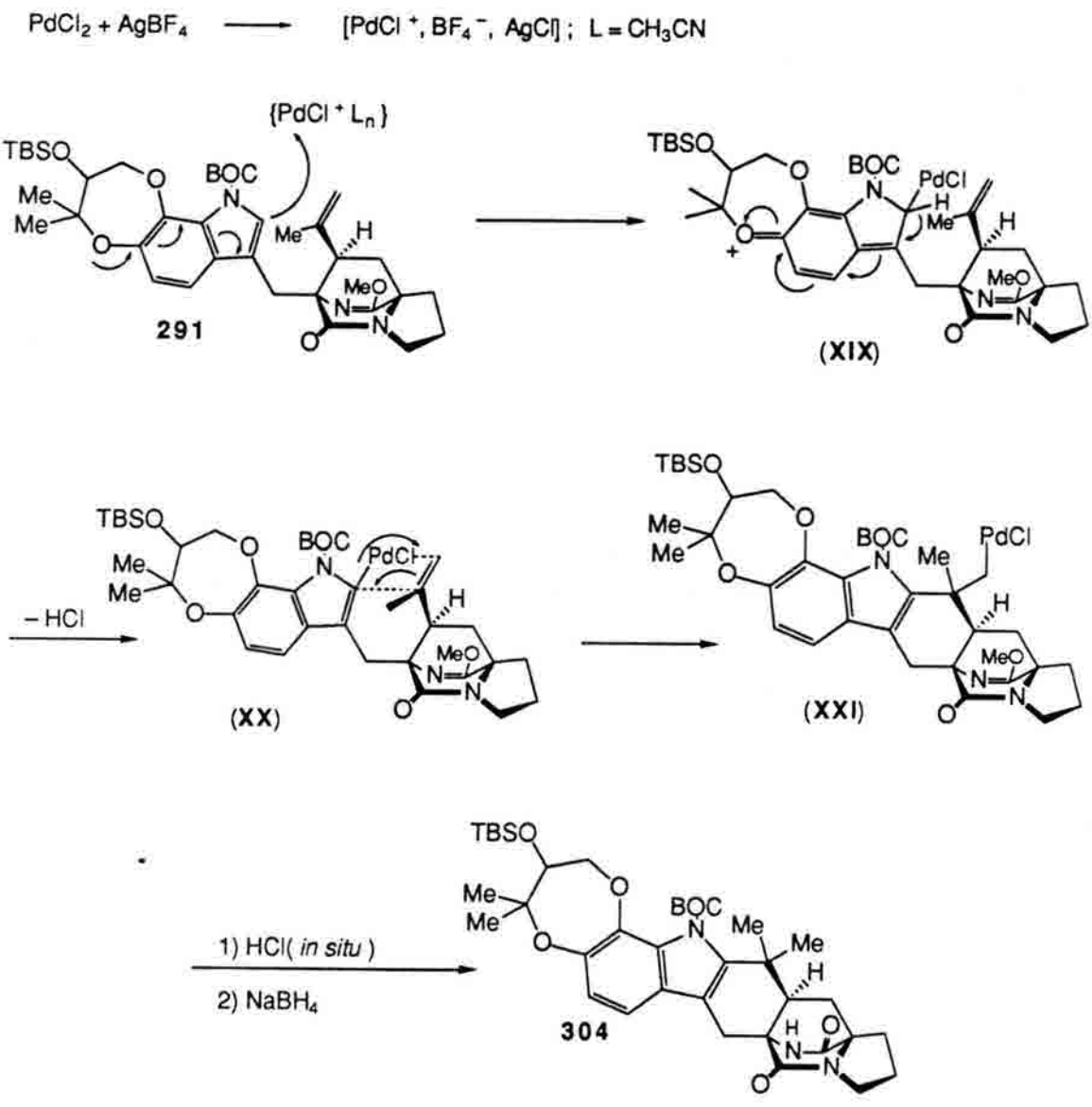
The byproduct **305** does not cyclize at all under the same conditions. We also found that the treatment of the lactim ether protected heptacycle (**306**) could not be deblocked to the free lactam with $PdCl_2$ and $AgBF_4$. This implies that the reason for the cleavage of the lactim ether is the HCl produced in the cyclization.

Trost theorized that the cyclization mechanism was either a Heck-type arylation or the electrophilic aromatic substitution of a palladium-complexed olefin. In his very detailed treatise, there was evidence to support both possibilities. However, a few points need to be made. Since that report there have been a number of investigations where a Heck

arylation has been enhanced with a silver salt.[119] Additionally, it is known that electrophilic aromatic substitution reactions involving olefins do not work in the presence of a Lewis acid. Strong protic acids are needed to effect the reaction. In fact, they demonstrated this quite effectively when Trost failed to form any cyclized products with numerous Lewis acids (boron trifluoride etherate, aluminum chloride, mercuric acetate, stannous chloride, stannic chloride, zinc chloride, magnesium bromide, titanium tetrachloride, and lead tetraacetate). It is possible that the palladium chloride and the silver tetrafluoroborate react to form a more powerful Lewis acid since, an incubation period involving these two reagents is needed prior to the introduction of the substrate. Trost and Fortunak found no reaction in other mixed metal systems with palladium chloride (e.g boron trifluoride , aluminum chloride, stannous chloride, stannic chloride, titanium trichloride). If our supposition about the enhanced basicity (nucleophilicity) of the 2-position of our indole **291** is correct (see Scheme 97), then **291** is perfectly disposed to undergo the Heck arylation. The indole initially reacts with the palladium(II) species providing the organopalladium(II) intermediate that subsequently inserts the olefin and eliminates the palladium. The normal course of this reaction is for the olefin to add to the least substituted position, but Trost argued that the six-membered ring is geometrically less strained than the seven-membered ring (Scheme 99).

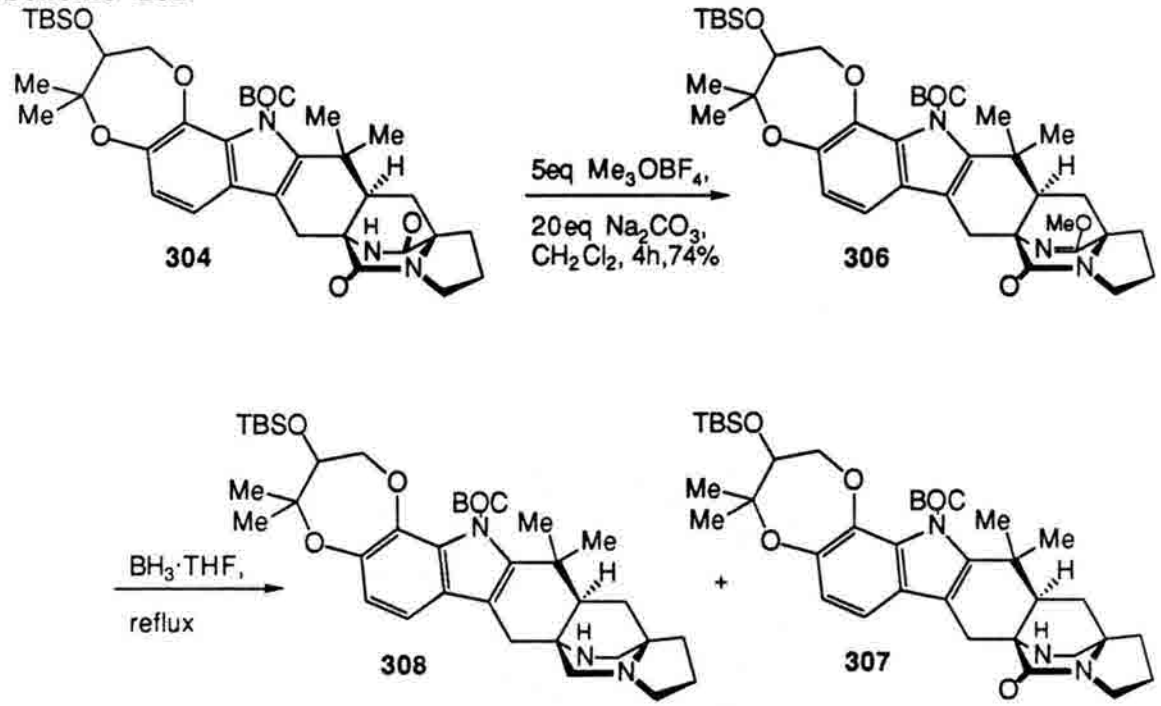
In the next stage (the reduction), we would have to distinguish between the tertiary lactam and a secondary lactam. We took the cyclized product **304** and treated it with Me_3OBF_4, obtaining the lactim ether **306**. This product was then subjected to the reduction procedure of Williams,[104] but it proved fruitless. The conditions were varied in numerous ways, but no desired compound was ever found. The reaction either gave a gross mixture of decomposition products or the undesired reduction products **307** and **308** (Scheme 101).

Scheme 100



Additional experiments were also attempted with this substrate, including the use of $BH_3 \cdot SMe_2$, but this gave similar results. An attempt was made to convert the lactam of **304** to a thiolactam,[120] with the aim that it could then be reduced off with Raney nickel. However, the thiolactam was not found and only the lactam **305** was formed.

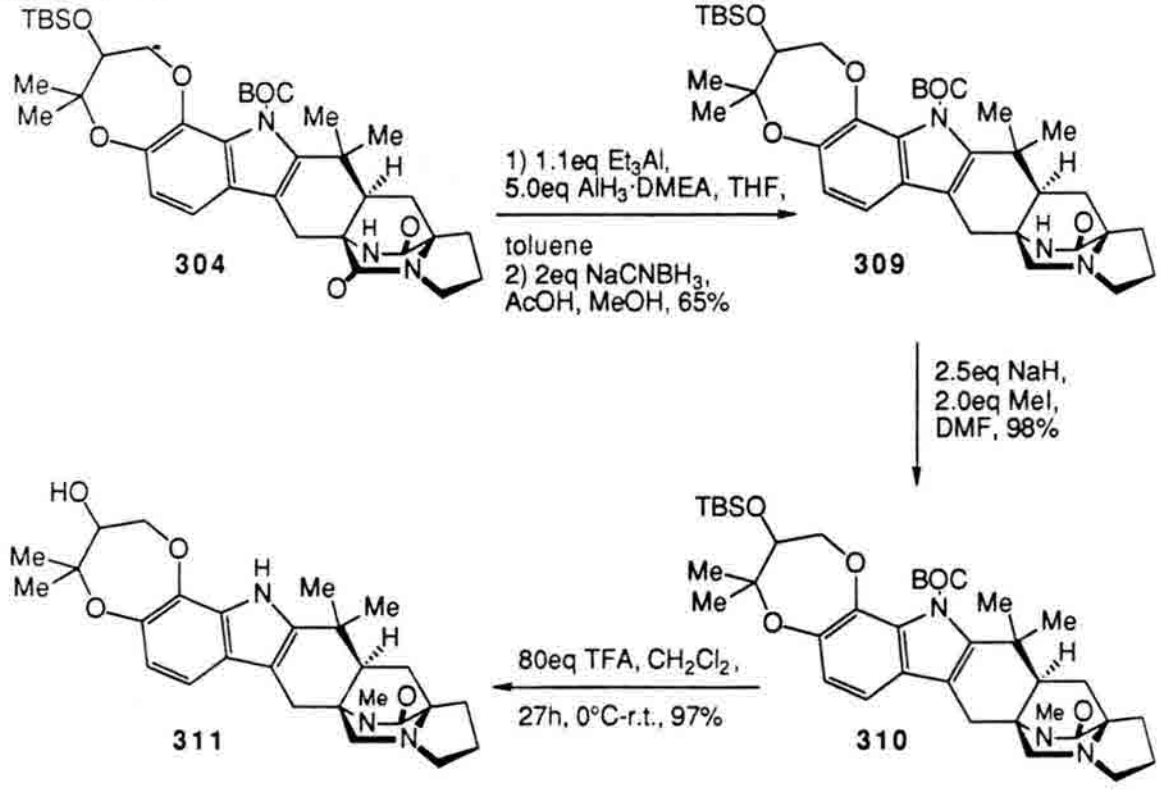
Scheme 101



At this time, work with this substrate was abandoned in an attempt to effect the reduction more directly. There are many ways reported in the literature to reduce tertiary amides, but few methods that will do this selectively in the presence of a secondary amide. It has been reported that $NaBH_4$ in t-BuOH and MeOH could reduce a tertiary amide in the presence of a secondary amide,[121] but this procedure failed on the piperazinedione **304**. In 1990 it was reported that tertiary amides could be reduced with sodium borohydride-bis(2-bromoethyl)selenium dibromide.[122] Apparently, the borohydride reacts with the bis(2-bromoethyl)selenium dibromide [123] providing a complex similar to $BH_3{\cdot}MeS_2$ but, this reaction also failed on **304**. The most promising method was with alane (AlH_3). In 1991 Martin *et al.*,[124] used alane to reduce a tertiary amide in the presence of an oxindole (secondary amide). This relied on the known rate difference in the reaction of this reagent between secondary amides and tertiary amides.[125] Alane can be prepared in a number of ways.[125b,c] It seemed that the DMEA–alane/toluene [125b] method proved superior. However, our initial experiments with this reagent gave only poor results. It seemed that difference in the rate of reduction between the two amide functionalities was not large

enough; and the secondary amide was being reduced as well as the tertiary amide. This was probably due to the sterically hindered tertiary amide, because the molecule is sufficiently twisted such that the *gem* -dimethyl groups effectively block the β– face of **304** relative to the α– face (Scheme 102). This explanation could also be invoked for the failure of **306** to reduce in the desired manner. This setback led us to modify the procedure of Martin by treating the starting piperazinedione with Et_3Al, with the aim that this reagent would form a complex with the the secondary lactam and leave the tertiary lactam open to reduction by AlH_3. This idea worked. The piperazinedione **304** was pretreated with Et_3Al, followed by five equivalents of AlH_3, and after two hours the reaction mixture was quenched with $NaCNBH_3$, AcOH and MeOH to provide **309** in 65% yield. This reduced product was easily alkylated with MeI affording the N-methylated product **310** in 95–98% yield. This product was subsequently deblocked with eighty equivalents of trifluoroacetic acid in dichloromethane to yield the penultimate product **311** in 97% (Scheme 102).

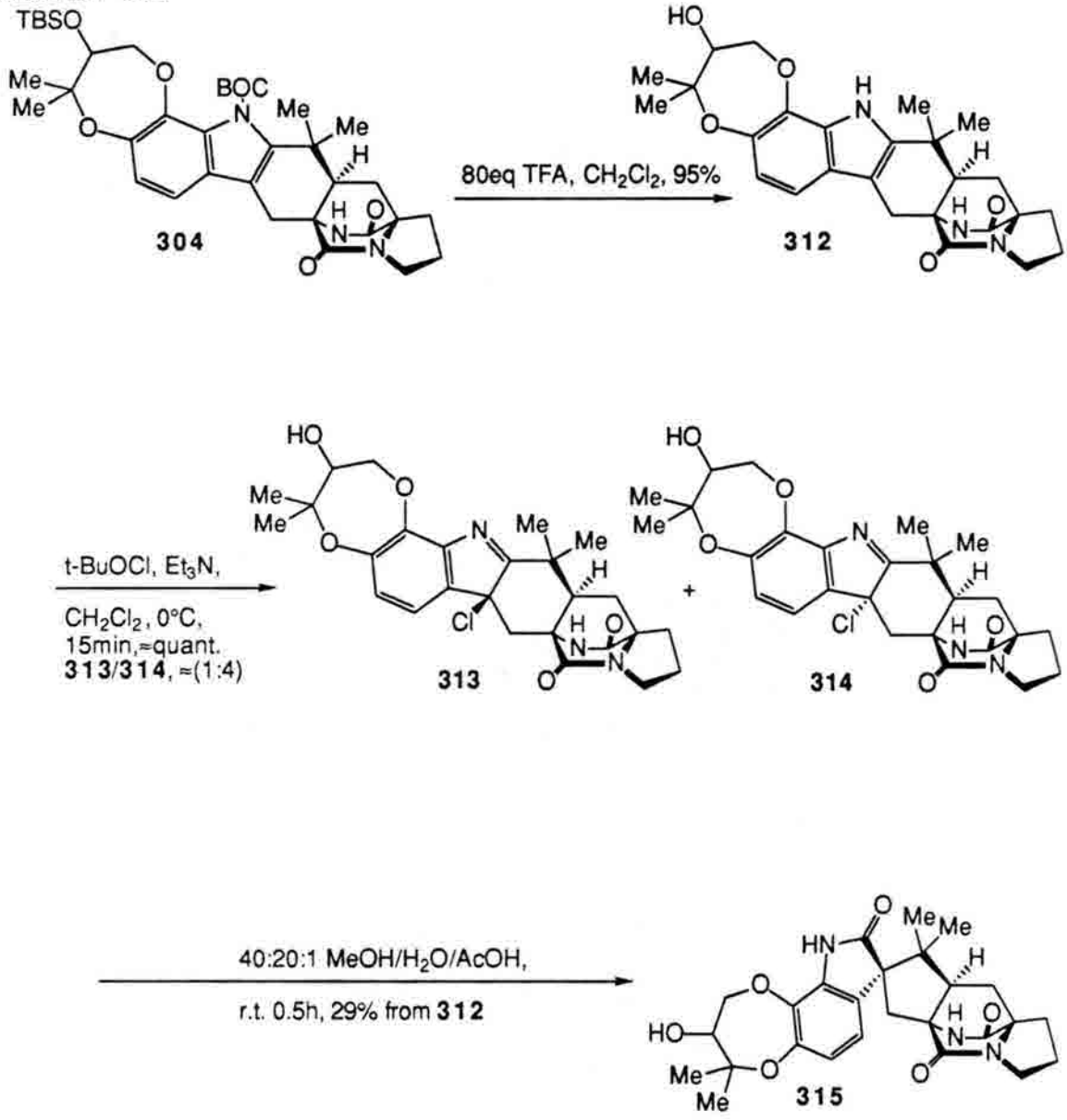
Scheme 102



We were now very close to the final product, and were concerned about the efficacy of the oxidative pinacol type reaction, employing the acid-catalyzed rearrangement of the intermediate chloroindolenine.[24c,41,126] There was the possibility that a stabilized oxonium would hinder the reaction in a similar way that strong acid hindered the cationic cyclization (see Scheme 97). Our fears about this possible difficulty were somewhat ameliorated by the knowledge of an alternative procedure that employed OsO_4·pyridine.[16,127] When we treated **311** with t-butylhypochlorite and triethylamine, there was an almost an instantaneous reaction. We observed the total disappearance of starting material and the appearance of two spots (TLC) that we assumed were the diastereomeric chloroindolenines. The relative amounts were in line with what we expected from the reaction on either the more hindered β– face or the less hindered α– face of **311** (≈1:2). We subjected the mixture to the standard rearrangement procedure employing a refluxing solution of acetic acid, water and methanol, but were greatly disappointed when the intermediate products slowly decomposed (many bands in the PTLC). In fact, repeated attempts under these conditions gave no desired products. This was a major blow, but problems of this sort were not unprecedented. On the way to the total synthesis of isopteropodine (**29**) and pteropodine, Martin reported[124,128] difficulties with this same transformation. Their solution involved treating the chloroindolenines with silver perchlorate in methanolic perchloric acid. This method was attempted on our substrate **311**, but unfortunately it failed to produce any desired product. So we switched gears and tried the osmium tetroxide reaction. The mechanism of this reaction is straightforward. The osmium tetroxide adds across the indole double bond producing a diol that does a classical pinacol rearrangement to provide the oxindole. This procedure was attempted on **311**, but it was another total failure. After one day, there remained a substantial amount of starting material together with four unidentifiable products. At this point we were getting a little nervous, so we decided to step back and rethink our plan. There was a concern that perhaps what we thought were the diastereomeric chloroindolenines were in fact either N-

chloro amines or some other oxidized compound.[129] In support from this was the finding of Merck & Co; that paraherquamide A (**1**) was readily oxidized to an amide or other products. A ^{1}H NMR spectrum of the chromatographed intermediate (chloroindolenine) was unidentifiable. However, it is known that chloroindolenines can be sometimes unstable. It was possible that it had just undergone air oxidation. On top of that, Winterfeldt [126b] found no difficulty in producing a chloroindolenine in a molecule that contained a tertiary amine. In any case, we decided to try the pinacol type rearrangement before the reduction step; this might be an alternative route or at least help us find a solution. The piperazinedione **304** was easily deblocked to provide the amide **252** in 95% yield. This compound was treated with t-butylhypochlorite and triethylamine in the same manner as before, and it proved quite interesting. The reaction was extremely rapid, producing two products **313/314** with Rf values similar to the products produced from **311**. They were also in a ratio of ≈1:4 as opposed to the 1:2 observed earlier. This simple result led us to believe that we had in fact formed the chloroindolenines previously, since the change in the ratio of products could be explained by the increase in steric hindrance on the β– face(caused by the amide carbonyl). A quick inspection of the ^{1}H NMR of the crude mixture (**313/314**) indicated that they were indeed the chloroindolenines. We at first tried the silver perchlorate, methanolic perchloric acid method but no desired product was formed. Switching to a milder MeOH/H_2O/AcOH system, (stirring at room temperature) an oxindole compound (**315**) was formed in 29% yield. This was encouraging, but it appeared to be the wrong epimer. This conclusion was reached by comparing the ^{1}H NMR spectra of **315**, (–)-paraherquamide B (**1**), and the model oxindole **103**. The gem dimethyl signals of **315** were shifted upfield more than was expected. They were similar to those found in the spectrum of the undesired **104** (Scheme 103).

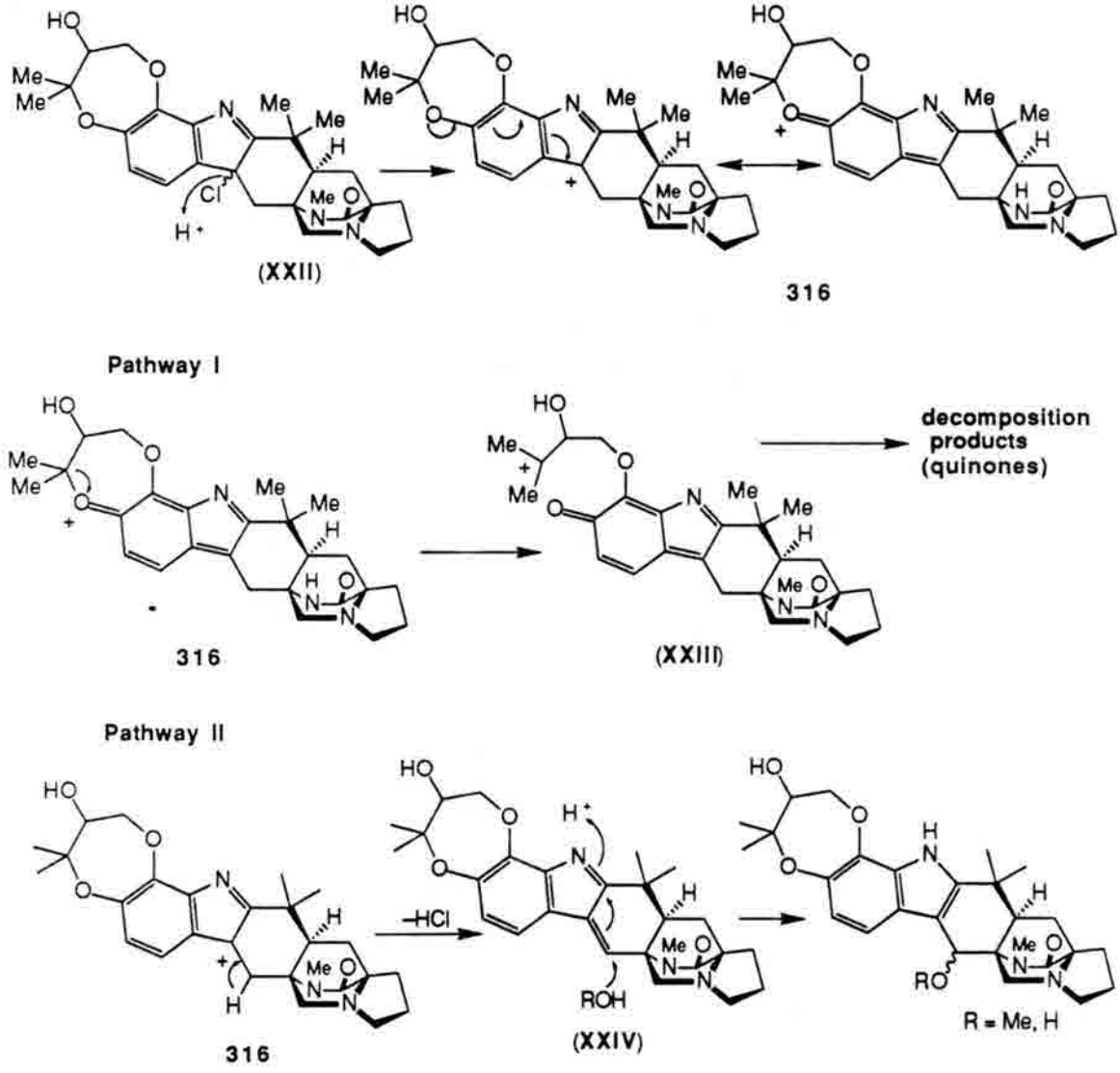
Scheme 103



At this point, we had decided to go back to our original approach, since we were confident that a method could be found to produce the desired results. Treatment of the monooxopiperazine **311** with *tert*-butyl hypochlorite and triethylamine exactly as before gave the same two products. These were quickly analyzed (crude) by ^{1}H NMR and found to be chloroindolenines as hypothesized (the ^{1}H NMR mimicked **313**,**314**). We were now beginning to understand what was occurring in this problematic step. After a careful reexamination of the decomposition products obtained from the attempted pinacol type

rearrangement, we determined that there were mainly two mechanistic pathways, and that they were in direct competition with the desired process. Both processes involve the intermediacy of the oxonium stabilized tertiary carbocation **316**. In pathway **I**, this oxonium decomposes to quinone type products, while pathway **II** involves an elimination process (E1) followed by an S_N2' type reaction of the solvent (Scheme 104).

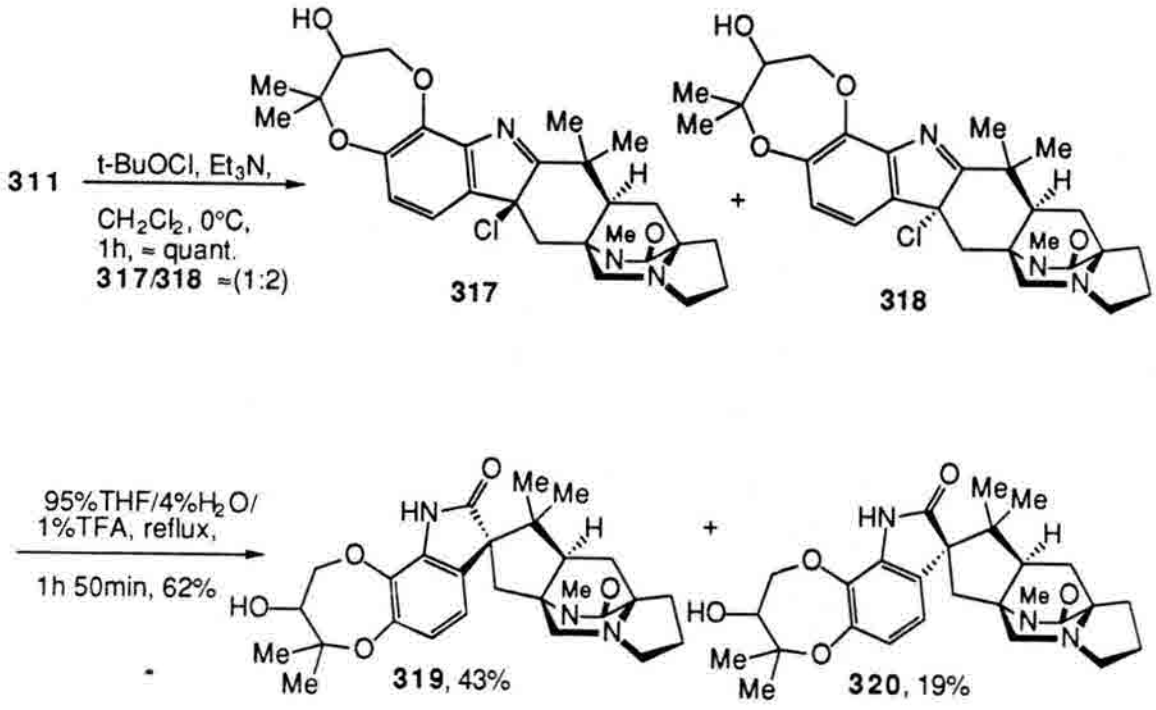
Scheme 104



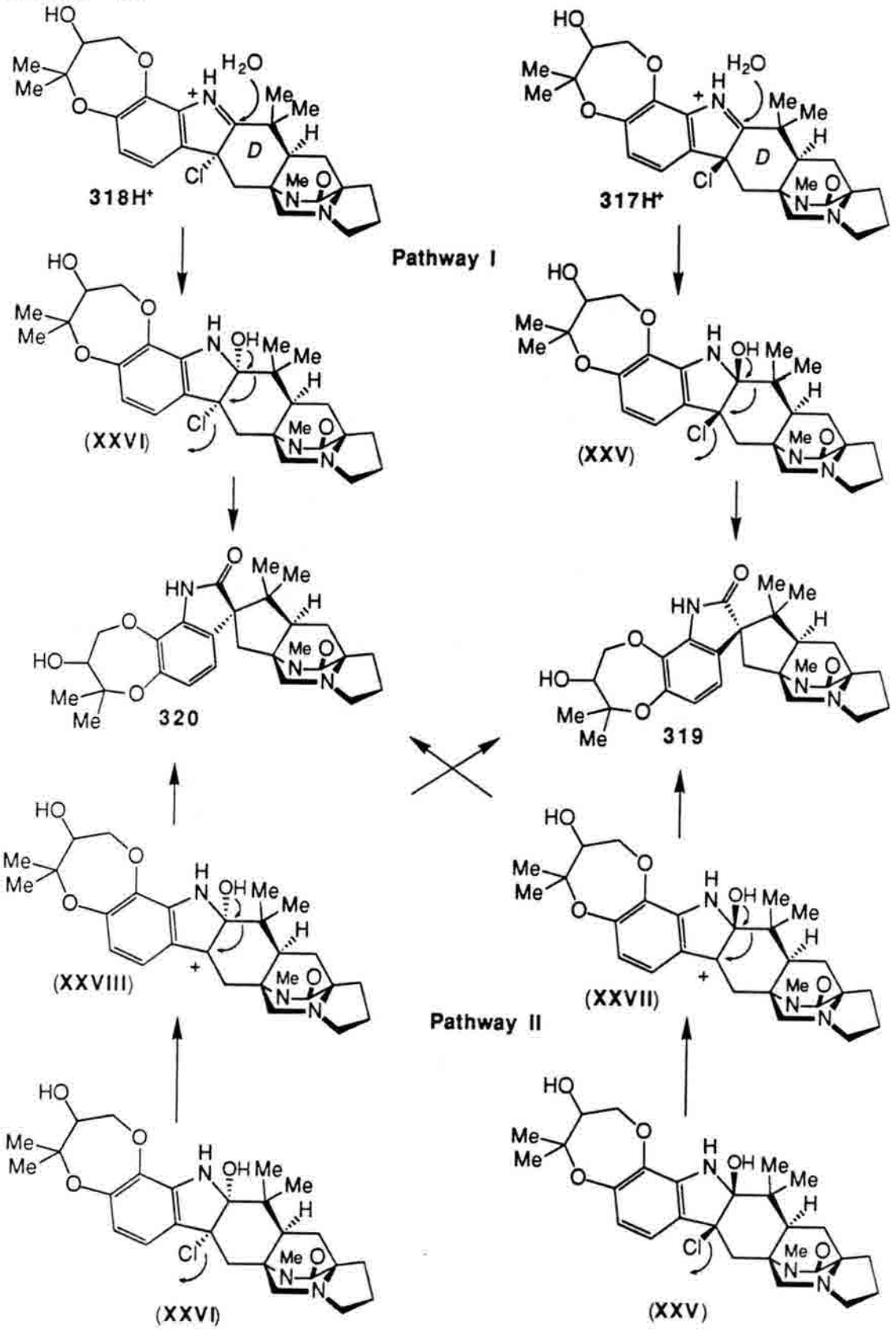
The problem was to control the reaction conditions minimizing these two pathways and at the same time, maximize the pinacol-type rearrangement. Mechanistically, this reaction is a bit more complicated. Under these reaction conditions (MeOH, H_2O, AcOH) it is highly likely that the oxidative spiro-cyclization was going through an oxonium-stabilized benzylic

carbocation similar to intermediate **316** depicted in Scheme 104. This is likely for two reasons. First, the solvent system (MeOH, H_2O,AcOH) is one of the best known systems for stabilizing a positive charge.[130] Reactions in polar protic solvents are known to go through E1 or S_N1 type processes. Second, we know that this must be occurring because the yield of **315** was greater than that allowed by the chloroindolenines. The ratio of chloroindolenines was ≈ 4:1 but the yield of **315** was 29%, implying that the reaction was not entirely (at least) stereospecific. According to the proposed mechanism, the chloroindolenine **313** is the precursor of oxindole **315**. There have been conflicting reports in the literature on whether this type of rearrangement is at all times stereospecific.[131] A detailed and rigorous study [132] involving the isolation and separation of the two diastereomeric chloroindolenines derived from yohimbine demonstrated that this reaction can be entirely stereospecific. Alternatively, by varying the conditions slightly (increasing the solvating power of the reaction medium), each of these chloroindolenines formed two rearranged products, implying that the chloroindolenine went by way of a carbocationic intermediate. This is what seems to have occurred in the production of **315**. With these thoughts in mind, we thought that by going to a less polar solvent system, we could minimize the side reactions involving the stabilized carbocation, and at the same time increase the stereospecific nature of the pinacol-type rearrangement (Scheme 105). Treatment of **311** with t-BuOCl and triethylamine in dichloromethane, provided the two chloroindolenines **317** and **318**. The solvent was removed and the crude reaction mixture refluxed with a solution of 95% tetrahydrofuran, 4% H_2O and 1% trifluoroacetic acid. To our great delight, we obtained a 62% yield of oxindole products (43% of the desired **319** and 19% the epi-product **320**). The epi **320** was easily distinguishable from the desired **319** by the upfield shift of the gem dimethyl signals in the ^1H NMR spectrum. The relative amounts of both products imply the stereospecific nature of the cyclization under these conditions.

Scheme 105


311
t-BuOCl, Et3N,
CH2Cl2, 0°C,
1h, ≈ quant.
317/318 ≈(1:2)
317
318
95%THF/4%H2O/
1%TFA, reflux,
1h 50min, 62%
319, 43%
320, 19%

Scheme 106


318H+
317H+
Pathway I
(XXVI)
(XXV)
320
319
(XXVIII)
(XXVII)
Pathway II
(XXVI)
(XXV)

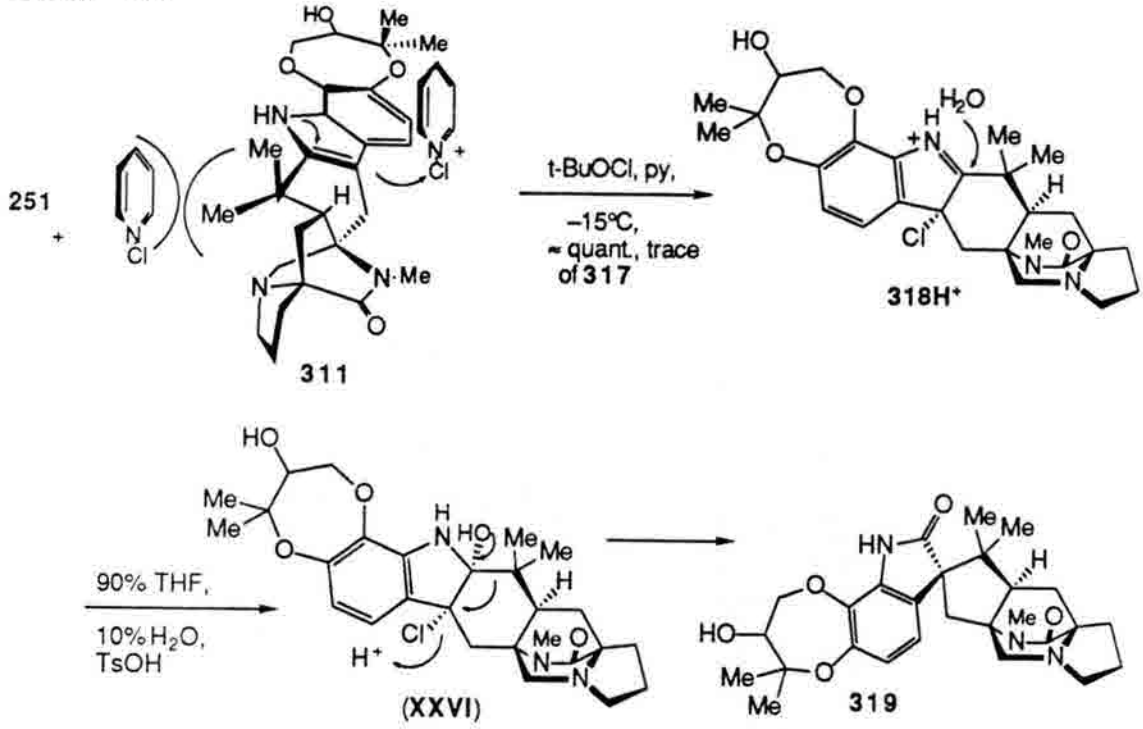
The two generalized competing mechanisms are outlined in (Scheme 105). Pathway **II** involves the intermediacy of a carbocation (an S_N1 process) resulting in a scrambling of the final oxindoles. Pathway **I** has more S_N2 character, allowing the reaction to proceed in a more stereospecific manner.

There are a few observations worth mentioning about this mechanism. First, both pathways presume that the water module attacks the imine from the same side as the chloro group. *Anti*-attack on the imine is not as likely because of certain stereoelectronic effects. The addition of water to the α– face of **317H⁺**, while putting the *D* ring in a stable chair configuration would also place the C-Cl and $(CH_3)_2C$-C (migrating bond) in an unfavorable *syn*-alignment. The addition of water to the β– face of **318H⁺** would result in an unfavorable boat configuration for ring *D*, and the required bonds would again have a *syn*-alignment. Second, the details of the second step in both pathways remains in question. It is unknown at what stage the carbon–carbon bond migrates, relative to the formation of the oxindole carbonyl. Interestingly, it is thought that in the classical pinacol rearrangement [133] the carbon–carbon bond migrates before the alcohol reverts to the carbonyl, that is, it is a strictly stepwise reaction.

If our assumptions about the above mechanism were correct, then we could increase the ratio of desired oxindole **319** to undesired **320** simply by finding a method that would increase the ratio of chloroindolenines (**318**:**317**). As was previously mentioned, the α– face of **311** is considerable more hindered than the β– face. This was demonstrated quite effectively by the difficulties encountered in the reduction of **304**. Perhaps by increasing the steric hindrance of our chlorinating agent, it would favor attack at the β– face thus providing a greater amount of **318**. When **311** was treated with t-BuOCl in pyridine instead of triethylamine, the desired chloroindolenine **318** was produced. The *tert*-butyl hypochlorite formed a bulky complex with the pyridine delivering the chlorine to the β– face of **318**, and only a small amount (≈ 5%) of the undesired **317** was formed. This product was then treated with a modification of our earlier solvent system. The crude

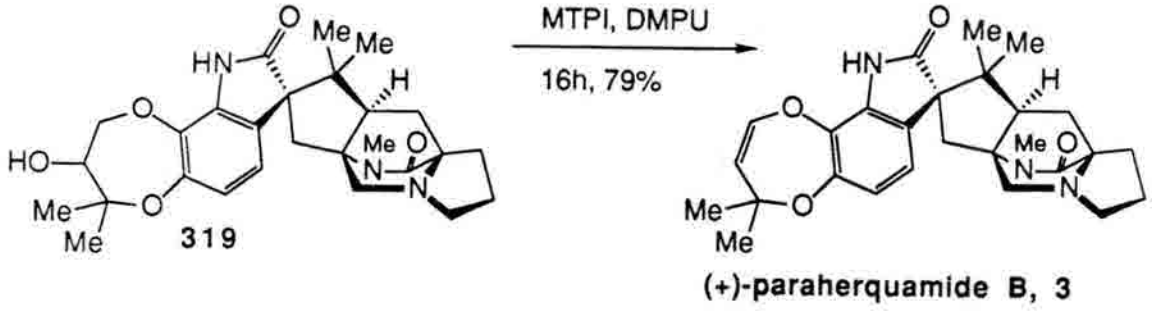
318/317 mixture was refluxed with a solution of 90% tetrahydrofuran, 10% H_2O and five equivalents of toluenesulfonic acid to give the desired oxindole **319** in 74% yield (from **311**), but only 4% amount of the undesired **320** was formed (Scheme 107).

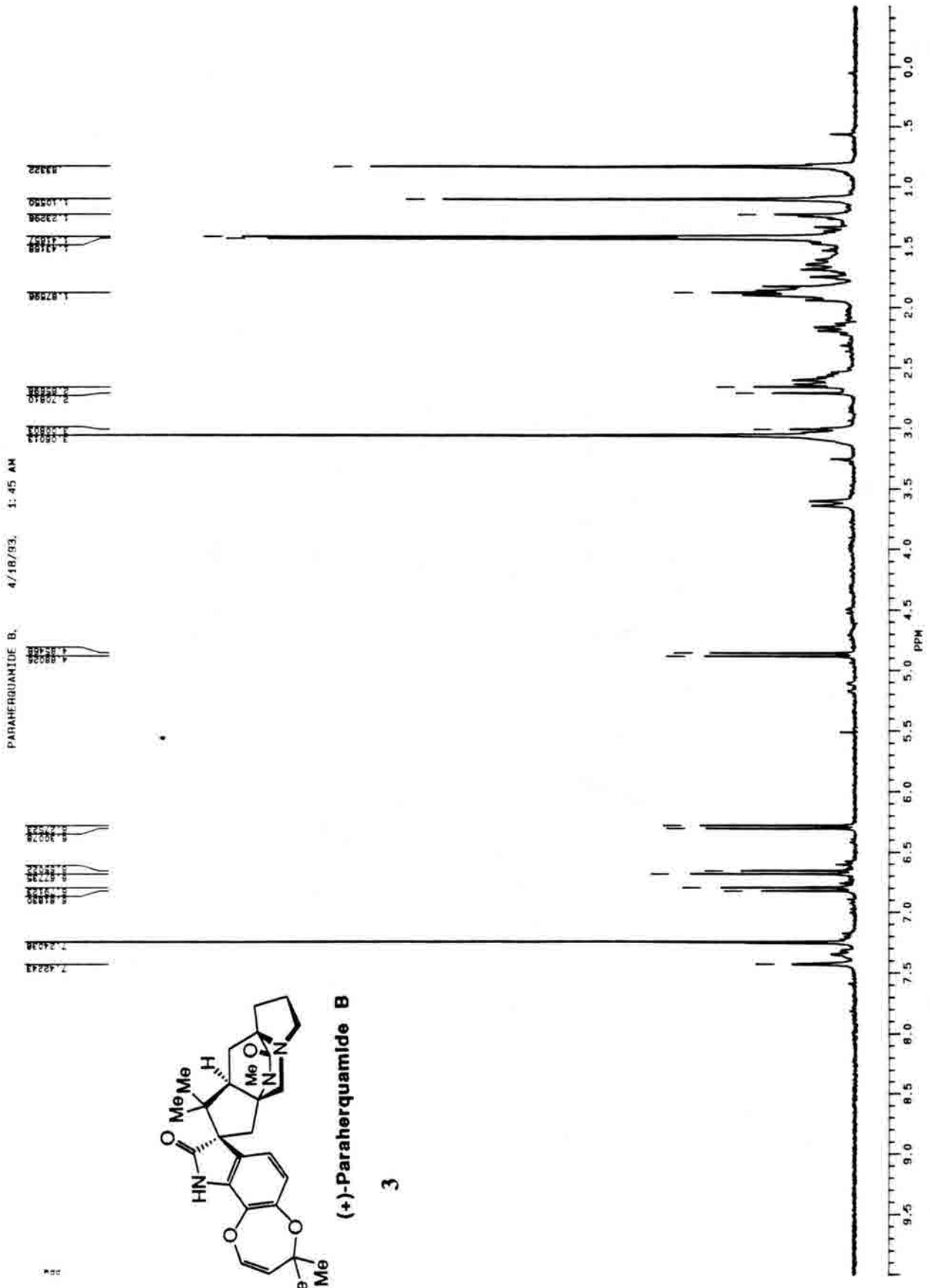
Scheme 107



It was now a simple matter to apply the dehydration procedure (MTPI, HMPA, 4h) to the alcohol **320**, producing (+)-paraherquamide B (**3**) in 29% yield. This was later optimized to give **3** in 83% yield. It proved to be identical in all respects to the natural product by comparison with a ^1H nmr supplied by Dr. John Ondeyka of Merck (Scheme 108).

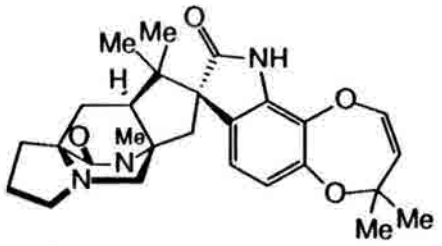
Scheme 108





(+)-Paraherquamide B

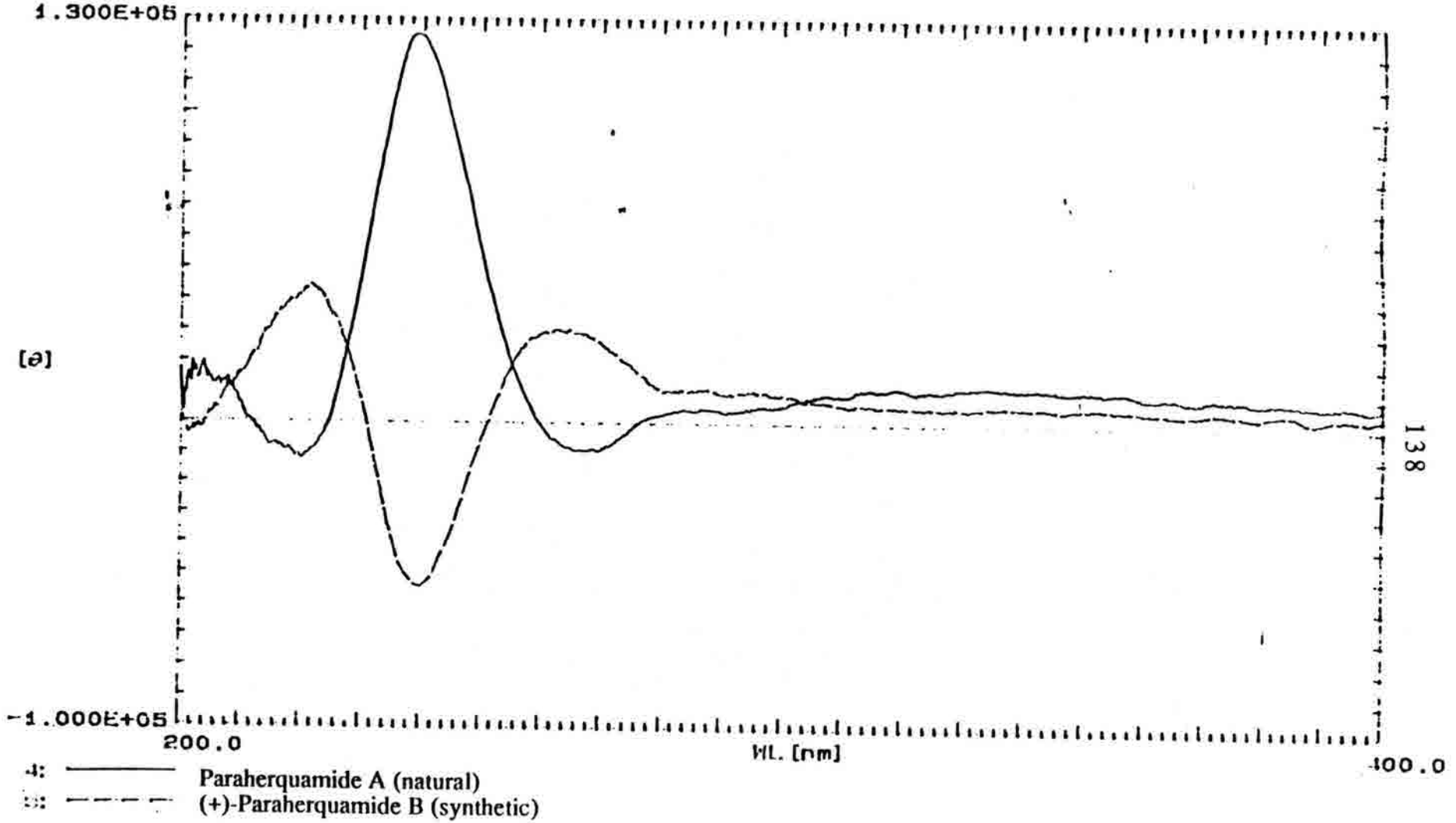
3



(–)-paraherquamide B, **2**

dichloromethane-D4

* Ethyl acetate



CD Spectra (CH_2Cl_2)

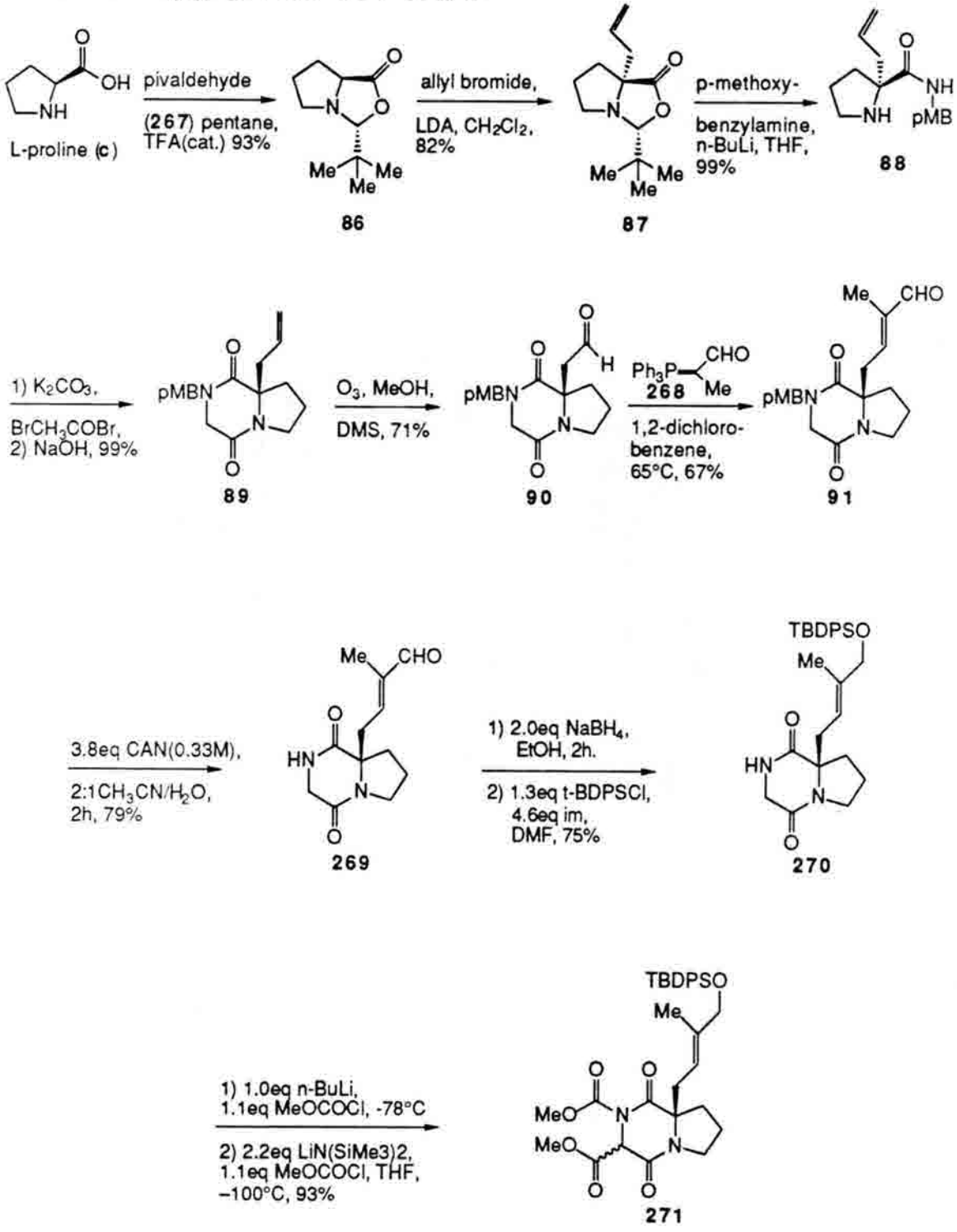
3.4 Summary of the Total Synthesis of (+)-paraherquamide B

The first stereocontrolled total synthesis of (+)-paraherquamide B was completed in 42 chemical steps (Scheme 109–111). The synthesis was a convergent one, starting from S-proline and vanillin with an the overall yield of 1.4% from S-proline.

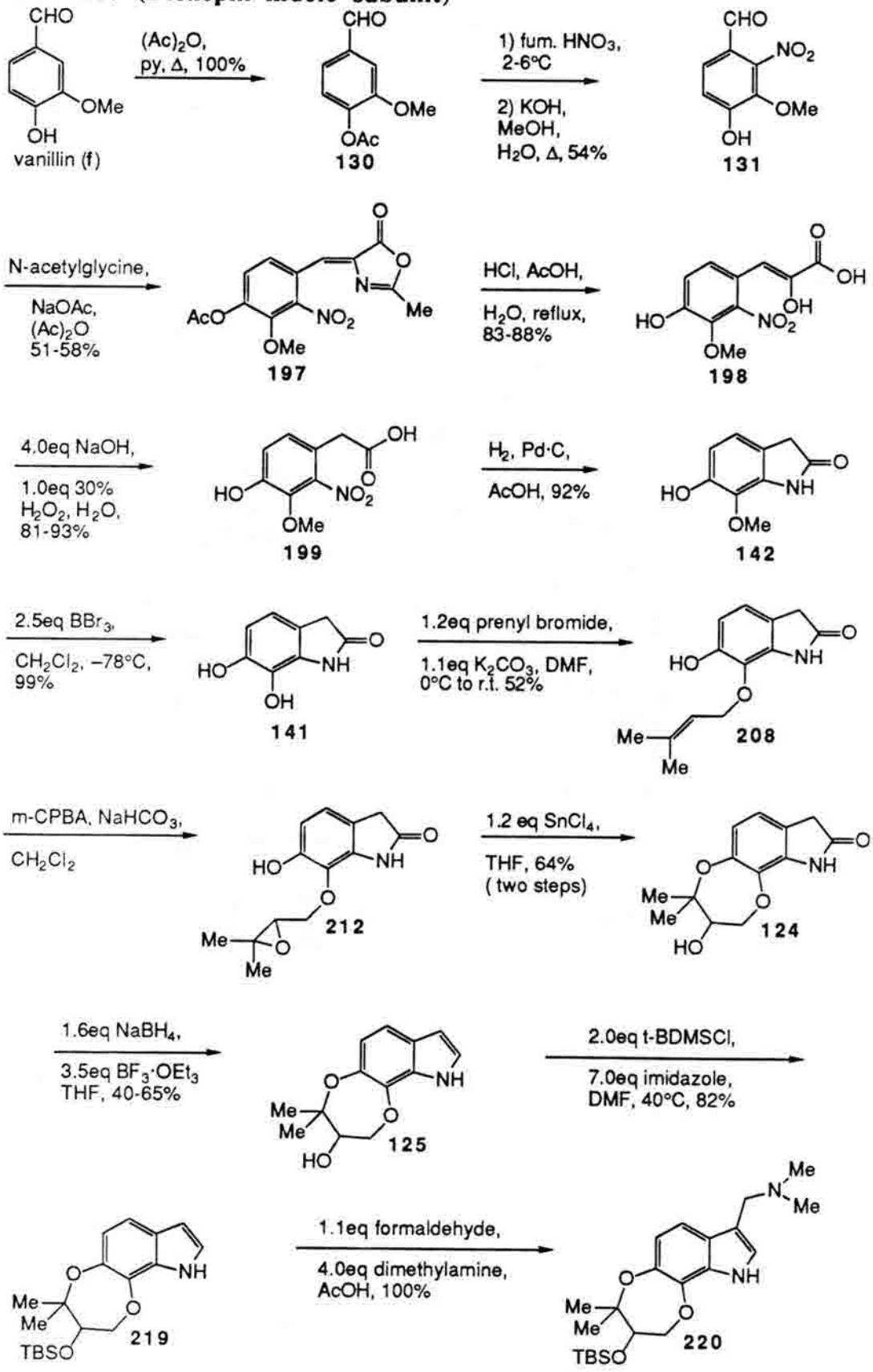
Key (novel) features of this synthesis include: A new method to effect reduction of unprotected oxindoles to indoles (Scheme 110, see **125**); A unique application of the Somei/Kametani reaction that concomitantly effected a desired demethoxycarbonylation (Scheme 111, see **272**); The use of a lactim ether as a protecting group for a lactam (Scheme 111); A high yielding entirely stereocontrolled S_N2' reaction (Scheme 111, see **291**); A mild Pd(II) mediated cyclization reaction that fortuitously deblocked the lactim ether protecting group (Scheme 111, see **304**); The reduction of a highly hindered tertiary lactam in the presence of an unhindered secondary lactam, using the coordination ability of triethylaluminum (Scheme 111, see **311**).

Finally, we learned that the 6-phenolic oxygen holds the key to the reactivity of many of the synthetic paraherquamide B precursors. Additionally, it is this same oxygen that may also play a pivotal role in the biosynthesis of the paraherquamides and marcfortines.

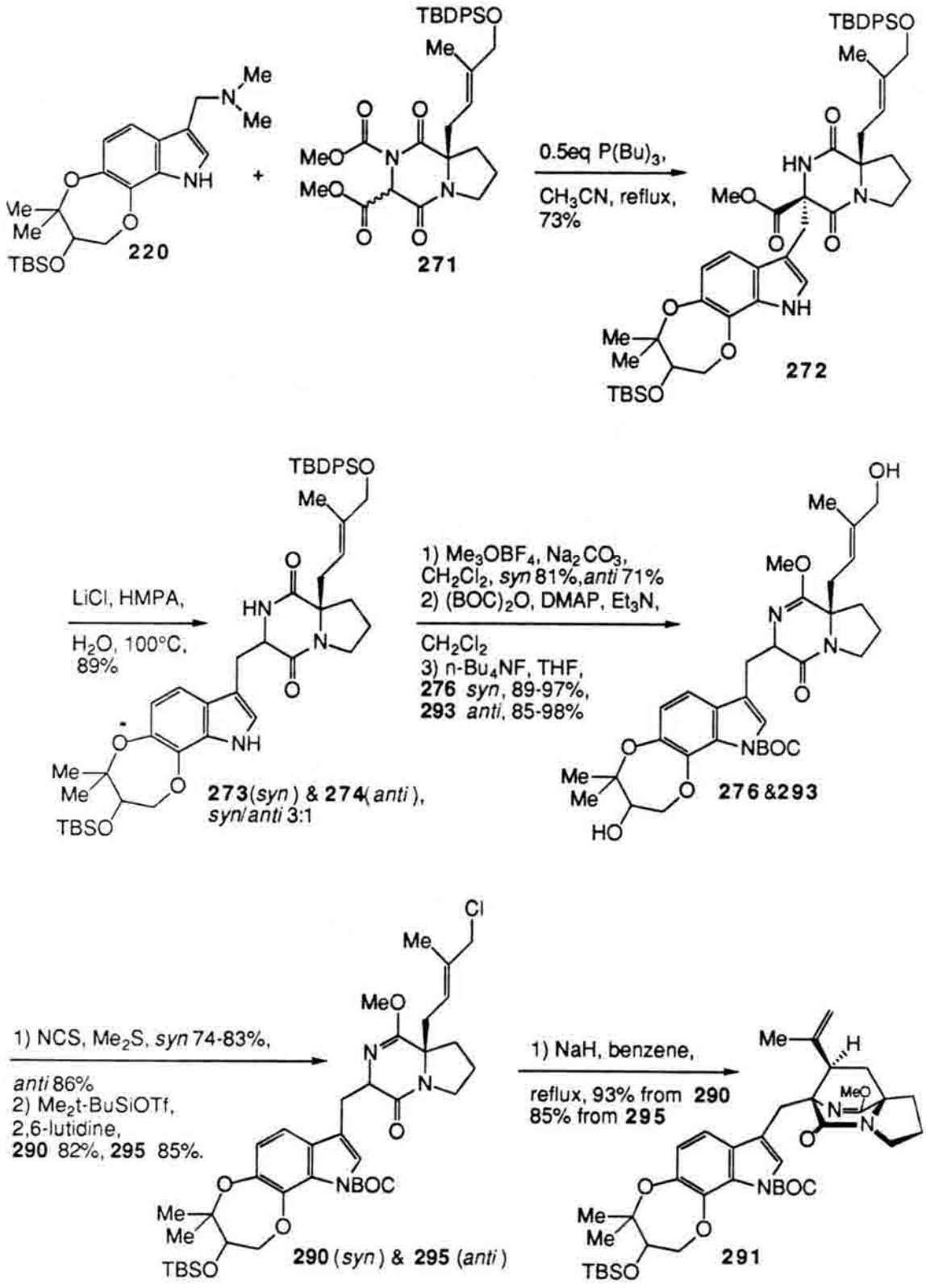
Scheme 109 (piperazinedione subunit)



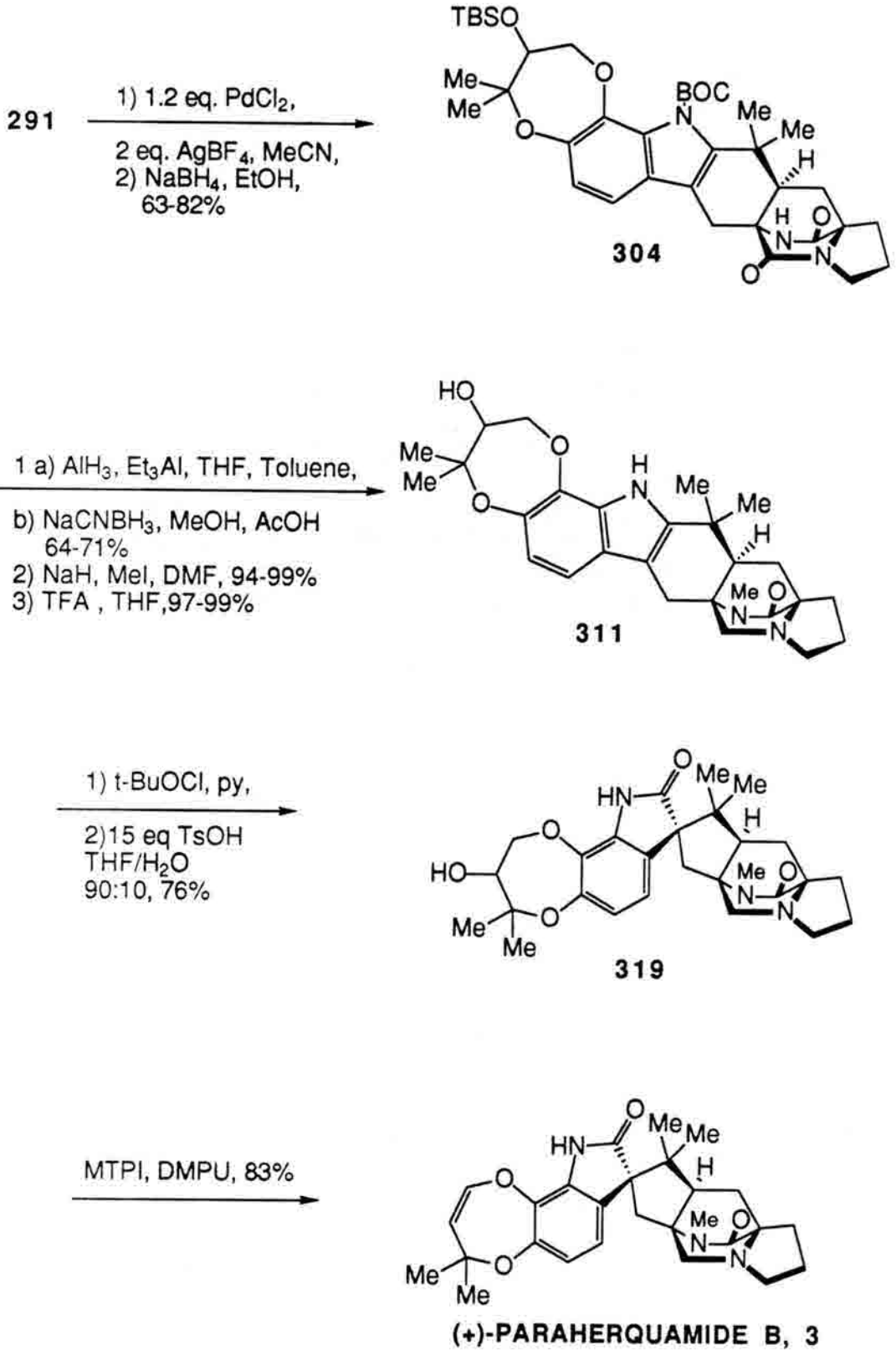
Scheme 110 (Dioxepin–indole subunit)



Scheme 111 (Paraherquamide B)



Scheme 111 continued



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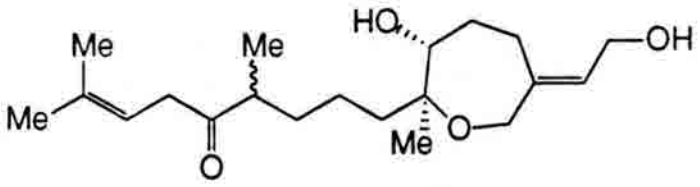

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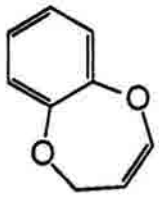

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CHAPTER FOUR

EXPERIMENTAL

General information

Melting points were determined by way of a Mel temp apparatus in open ended capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR was found with either a Bruker WP-270SY 270MHz or a Bruker AC300P NMR spectrometer. The chemical shifts were measured from residual $CHCl_3$ at δ 7.24 or from TMS at δ 0.0. IR spectra were recorded on a Perkin–Elmer 1600 FT IR. Mass spectrams were obtained on a V.G. Micromass Ltd. Model 16F spectrometer. High resolution mass spectra were obtained from the Midwest Center for Mass spectrometry in Lincoln Nebraska. Elemental analysis were obtained from M-H-W Laboratories, Phoenix Arizona. Optical rotations were recorded on a Perkin–Elmer 24 polarimeter at a wavelength of 589nm using an 1.0 decimeter cell of 1.0ml total volume.

Chromatography

Column chromatography and flash column chromatography were performed with silica gel grade 60 (230–400 mesh). Radial chromatography was performed with a Harrison research Chromatotron model 7924 using E. Merck silica gel 60 PF-254 containing gypsum; one, two, four and eight millimeter plates were used as needed. Preparatory thin layer chromatography (PTLC) was carried out with Merck Kieselgel 60 F_{254} precoated glass plates, (either 0.25mm or 0.50 mm). These plates were also used as a qualitative indicator for reaction completion, with ultraviolet light and heating with a solution of 5–7% phosphomolybdic acid. Additional visualization stains I_2/vanillin/Dragendorf were occasionally used.

Reagents and solvents

Solvents routinely distilled include; tetrahydrofuran from sodium benzophenone ketyl, diethyl ether from sodium benzophenone ketyl, carbon tetrachloride from calcium hydride, dioxane from sodium, benzene from sodium benzophenone ketyl, dichloromethane from calcium hydride, acetonitrile from P_2O_5. DMF was treated and stored over 3Å molecular sieves, as was benzene and toluene. DMS and 2,6-lutidine,

triethylamine and pyridine were all distilled prior to use. Potassium t-butoxide was purified by dissolving in THF and centrifuging the undissolved impurities; the concentration of the resulting solution was determined by measuring the weight difference of the crude reagent and the solid byproducts. Phenylselenium chloride was purified by sublimation. NCS was recrystallized from benzene. LiCl was dried and stored in the oven. All other reagents were commercial grade and used fresh without further treatment.

130

4-Acetoxy-3-methoxy-benzaldehyde (130)

A mixture of vanillin (1.02kg, 6.72mol, 1.0eq) and acetic anhydride (150mL, 10.7mol, 1.6eq) was refluxed for 24 hours, allowed to cool slightly, then poured with stirring into 5 liters of ice/water. The oil that separated, soon solidified, The crystalline white solid was collected, and washed thoroughly with water. yield; 1.31kg, 100%.

^{1}H NMR (300MHz) ($CDCl_3$) δ 2.31 (3H, s); 3.88 (3H, s); 7.19 (1H, d, J = 7.9Hz); 7.43-7.48 (1H, m); 9.27 (1H, s).

IR (neat) 1757, 1693, 1597, 1278, 1209, 1034 cm^{-1}.

(lit. ref. 48, m.p. 73-74 °C, recrystallized from water/MeOH).

130 **131**

4-Hydroxy-3-methoxy-2-nitro-benzaldehyde (131)

To stirring, cold (2 °C–6 °C) fuming HNO_3 (414mL, 9.85mol, 12.3eq) was added in small portions **130** (156g, 801mmol, 1.0eq). After the addition was complete the reaction mixture was stirred 10 minutes and then poured into 1.5 liter of ice/water. This procedure was repeated 5 more times (see Table).

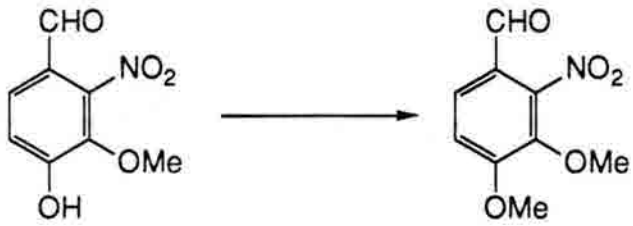
entry	1	2	3	4	5
acetylvanillin	152g	152g	151g	150g	256g
HNO_3	405mL	405mL	402mL	405mL	680mL

The "scrambled eggs" colored product from all six reactions was collected and washed with water. This wet crude product was refluxed in a 5 liter flask with CH_3OH (503mL), H_2O (503mL) and a 45% solution of KOH (619mL) for 15 minutes. The dark brown solution was slowly cooled and treated with HCl (conc.) until a brown solid was formed (pH≈3). This crude solid was dried and then taken up in EtOH (2.54L). The deep brown mixture was filtered to remove the solid impurities (5-nitrovanillin). The filtrate was then concentrated to dryness and the brown crystalline product, collected, dryed and recrystallized from water. yield; 575g, 55%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.98 (3H, s); 6.66 (1H, s, D_2O exch.); 7.21 (1H, d, J = 8.7Hz); 7.65 (1H, d, J = 8.4Hz); 9.81 (1H, s).

IR (neat) 3264 (br) 1676, 1596, 1433, 1200, 1039, 976, 906, 827, 813, 781, 643 cm^{-1}.

(lit. ref. 48a, m.p. 137-138 °C, recrystallized from ethyl acetate).



131 **132**

3,4-Dmethoxy-2-nitro-benzaldehyde (132)

To a stirred solution of **131** (55.7g, 283mmol, 1.0eq) and K_2CO_3 (65.6g, 475.0mmol, 1.7eq) in CH_3CN (131mL) was added dimethylsulfate (32.7mL, 350.5mmol, 1.2eq). The resulting mixture was refluxed for 30 minutes, cooled for 5 minutes and then treated with NH_4OH (261mL, 523mmol, 2eq). Water (200mL) was then added, and 45%KOH until the pH ≈ 12. The solution was acidified (HCl) and extracted with

CH_2Cl_2. The dark residue was run through a plug of silica chromatography; 3:2 hexane/ethyl acetate, yield; 30.7g, 51%. An analytical sample was recrystallized from ethyl acetate/hexane (brown crystalline solid).

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.95 (3H, s); 4.02 (3H, s); 7.13 (1H, d, J = 8.6Hz); 7.67 (1H, d, J = 8.6Hz); 9.80 (1H, s).

IR (neat) 1696, 1600, 1544, 1504, 1459, 1283, 1045, 960 cm^{-1}.

m.p.48–50 °C.

(lit. ref. 48b, m.p. 64 °C).

132 **133**

3,4-Dimethoxy-2-nitro-benzylalcohol (133)

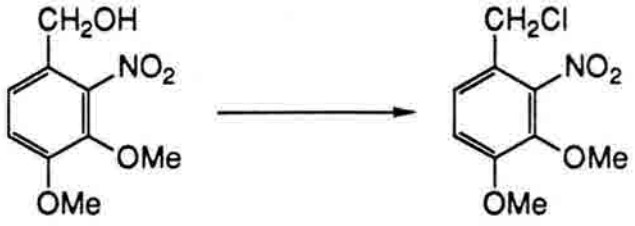
To a stirred solution of **132** (16.0g, 75.8mmol, 1.0eq) in EtOH (5.0mL) at 0 °C under N_2 was added $NaBH_4$ (1.43g, 38.0mmol, 0.5eq). The mixture was stirred for 18 hours, poured into a separatory funnel, washed with 1M HCl and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After concentrating the product was obtained as a yellow crystalline solid, pure enough for the next step. yield; 15.8g, 98%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 2.42 (1H, s, D_2O exch.) 3.92 (3H, s); 3.93 (3H, s); 4.56 (2H, s); 7.02 (1H, d, J = 8.6Hz); 7.18 (1H, d, J = 8.6Hz).

^1H NMR (300MHz) ($CDCl_3$) δ 2.91 (1H, br s, D_2O exch.); 3.86 (3H, s); 3.87 (3H, s); 4.51 (2H, s); 6.97 (1H, d, J = 8.6Hz); 7.12 (1H, d, J = 8.6Hz).

IR (neat) 3383, 2945, 1538, 1456, 1372, 1278, 1061, 1020 cm^{-1}.

(lit. ref. 51a, m.p. 68-69 °C, recrystallized from pet. ether).



133 **134**

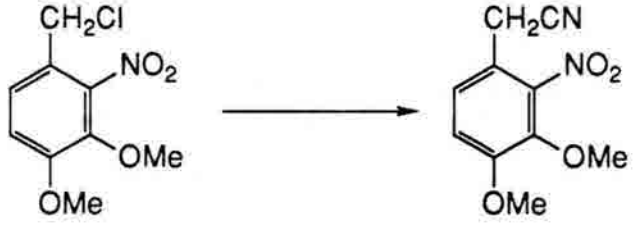
3,4-Dimethoxy-2-nitro-benzylchloride (134)

To a stirred solution of **133** (15.8g, 74.2mmol, 1.0eq) in benzene (300mL) at 0 °C, under N_2, was added thionyl chloride (10.8mL, 148.5mmol, 2.0eq) and 10 drops of pyridine. The reaction was kept for 32 hours. After washing with water, brine, drying over $MgSO_4$, and concentrating, a yellow oil was recovered. This was dissolved in CH_2Cl_2 and eluted through silica gel (3:2 hexane/ethyl acetate), to give a yellow waxy solid. yield; 17.3g, 100%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.92 (3H, s); 3.96 (3H, s); 4.54 (2H, s); 7.00 (1H, d, J = 8.6Hz); 7.20 (1H, d, J = 8.6Hz).

IR (neat) 2944, 1730, 1538, 1504, 1459, 1377, 1283, 1221, 1056 cm^{-1}.

(lit. ref. 51a, m.p. 58-59 °C).



134 **135**

3,4-Dimethoxy-2-nitro-benzylnitrile (135)

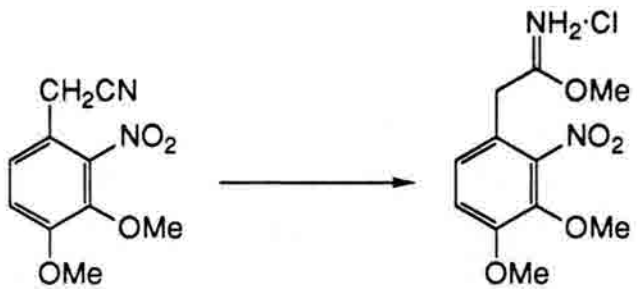
To a stirred solution of **134** (17.3g, 74.6mmol, 1.0eq) in CH_3CN (678mL) was added KCN (7.43g, 113mmol, 1.5eq) and a catalytic amount of 18-crown-6 ether. The resulting solution was refluxed for 18 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The crude oily black substance was filtered through a

plug of silica leaving an orange solid, which needed no further purification. yield; 15.9g, 96%.

^{1}H NMR (270MHz) ($CDCl_3$) δTMS 32.66 (1H, s); 3.70 (1H, s); 3.91 (3H, s); 3.94 (3H, s); 7.06 (2H, d, J = 8.6Hz); 7.27 (1H, d, J = 8.6Hz).

IR (neat) 1538, 1504, 1368, 1300, 1266, 1056 cm^{-1}.

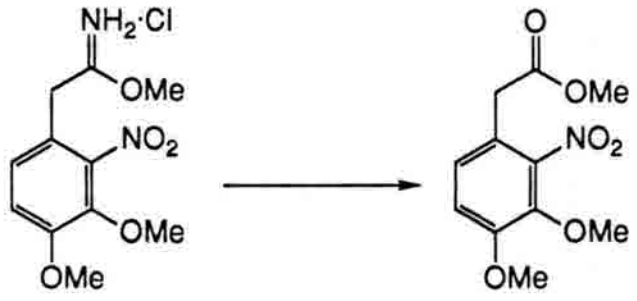
(lit. ref. 51a, m.p. 68-69 °C, colorless needles, recrystallized from water/EtOH).



135 **136**

Anhydrous HCl was bubbled through a stirred solution of **135** (15.9g, 71.7mmol, 1.0eq) in diethyl ether (220mL) and CH_3OH (11.6mL, 287mmol, 4.0eq) at 0 °C for five hours. The mixture was filtered and the crude imino–ether hydrochloride dried. yield; 15.9g. The filtrate was found to contain unreacted starting material. An additional amount of CH_3OH was charged to the flask and HCl bubbled through at 0 °C for 3 more hours. After filtering the yield was 4.79g The products (colorless needles) were combined and taken on to the next step. total yield; 20.7g, 99%. This salt was not characterized.

(lit. ref. 51, colorless needles).



136 **137**

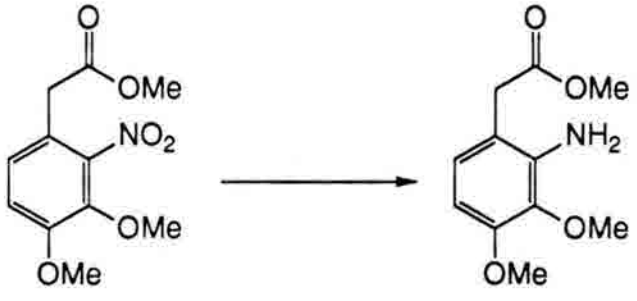
3,4-Dimethyl-2-nitro-methylphenylacetate (137)

A stirred solution of the **136** (15.9g, 54.7mmol, 1.0eq) in water (380mL) was gently refluxed for 2 hours. The reaction mixture was cooled and filtered. The filtrate was found to contain unreacted starting material, so it was resubjected to the same conditions, refluxing water (120mL) 3 hours. After filtration the two crops were combined. chromatography; column, yield; 14.8g, 100%, as an orange oily solid.

^{1}H NMR (270MHz) ($CDCl_3$) δTMS 3.61 (2H, s); 3.69 (3H, s); 3.91 (3H, s); 3.94 (3H, s); 6.99 (2H, d, J = 8.7Hz).

IR (neat) 2944, 1742, 1538, 1504, 1368, 1283, 1056 cm^{-1}.

(lit. ref. 51).



137 **138**

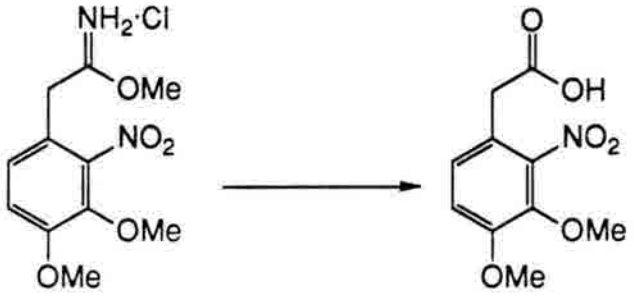
2-Amino-3,4-dimethyl-methylphenylacetate (138)

A stirred solution of **137** (14.8g, 61.5mmol, 1.0eq) in CH_3OH (300mL) and 5% Pd·C (1.0g) was hydrogenated (shaken) at 60psi for approx. 12 hours. The solution was filtered through celite and then through a plug of silica gel. yield; 11.4g, 83%. An analytical sample was recrystallized from ethyl acetate/hexane to give a crystalline red solid.

^{1}H NMR (270MHz) ($CDCl_3$) δTMS 3.52 (2H, s); 3.68 (3H, s); 3.82 (6H, s); 4.30 (2H, br s, D_2O exch.); 6.32 (1H, d, J = 8.5Hz); 6.79 (1H, d, J = 8.5Hz).

IR (neat) 3126 (br) 1691, 1640, 1464, 1351, 1096 cm^{-1}.

m.p. 196–197 °C.



136 **140**

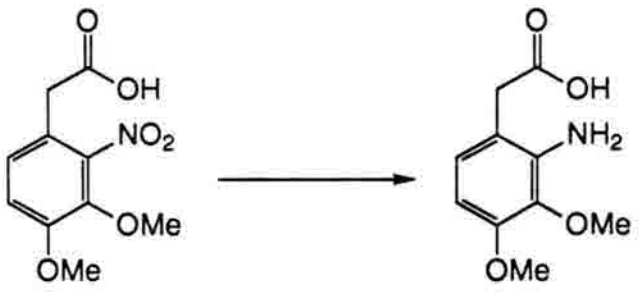
3,4-Dimethyl-2-nitro-phenylacetic acid (140)

A solution the **136** (276.2mg, 0.9501mmol, 1.0eq) in water (9ml) was stirred for 0.5 hours on the water bath. At this time HCl conc. (1.44ml) was added and the solution refluxed for 2 hours. The mixture was filtered and the brown resin crystallized under vacuum aspiration (in the flask). The filtrate (yellow crystals) were dried in the oven (120 °C). Both crops were recrystallized from boiling water, combined yield; 122.4mg, 53%.

^{1}H NMR (270MHz) ($CDCl_3$) δTMS 3.64 (2H, s); 3.89 (3H, s); 3.94 (3H, s); 7.00 (1H, d, J = 10.8Hz); 7.05 (1H, d, J = 10.8Hz); 8.35–9.20 (1H, s, D_2O exch).

IR (neat) 2944 (br), 1714, 1534, 1500, 1280, 1223,1058 cm^{-1}.

(lit. ref. 51, m.p. 143-146 °C, recrystallized from water).



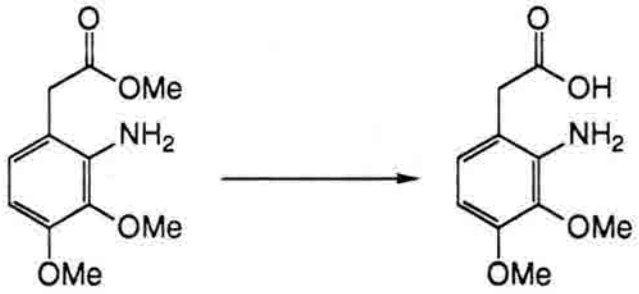
140 **139**

2-Amino-3,4-dimethyl-phenylacetic acid (139)

To a stirred solution of **140** (109.8mg, 0.4552mmol, 1.0eq) in CH_3OH (160ml) was added Pd·C (32.3mg). The mixture was placed under H_2 (60psi) for 19 hours. It was then filtered through celite to give 83.6mg of a crude solid. The crude was recrystallized from ethyl acetate/hexane, (orange solid). recovered yield; 47.3mg, 49%.

^1H NMR (300MHz) (acetone-D_6) δTMS 2.78 (1H, s, D_2O exch.); 2.86 (1H, s, D_2O exch.); 3.50 (1H, d, J = 1.1Hz); 3.81 (3H, s); 3.85 (3H, s); 6.67 (1H, d, J = 8.1Hz); 6.97 (1H, dt, J = 1.1, 8.1Hz); 9.50 (1H, br s, D_2O exch.).

IR neat 3426 (br) 2516, 1705, 1633, 1462, 1206 cm^{-1}.



138 **139**

2-Amino-3,4-dimethyl-methylphenylacetic acid (139)

To a stirred solution of **138** (11.43g, 50.74mmol, 1.0eq) in H_2O (697mL) was added conc. HCl (53.51mL) and gently refluxed for 2 hours. The mixture was cooled (refrigerated overnight) and the precipitate collected. After concentrating the filtrate the remaining residue was combined with the precipitate. yield; 9.81g, 100%.

^{1}H NMR (300MHz) (acetone-D_6) δTMS 2.78 (1H, s, D_2O exch.); 2.86 (1H, s, D_2O exch.); 3.50 (1H, d, J = 1.1Hz); 3.81 (3H, s); 3.85 (3H, s); 6.6.67 (1H, d, J = 8.1Hz); 6.97 (1H, dt, J = 1.1, 8.1Hz); 9.50 (1H, br s, D_2O exch.).

IR neat 3426 (br) 2516, 1705, 1633, 1462, 1206 cm^{-1}.

(lit. ref. 44)

139 **120**

1,3-Dihydro-6,7-dimethoxy-2*H*-indol-2-one (120)

A stirred solution of **139** (9.81g, 46.4mmol, 1.0eq) in THF (663mL) and DCC (9.49g, 46.4mmol, 1.0eq) at 0 °C under N_2 was stirred for 4 hours. Acetic acid (2.0mL, 34.82mmol, 0.75eq) was added to the cold solution and stirred an additional 2 hours. The resulting mixture was filtered to remove DCU, and the crude product isolated from the filtrate. It was recrystallized from hot water to give a faint yellow crystalline solid. yield; 5.74g, 64%.

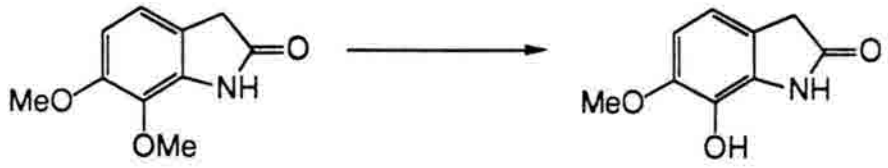
^{1}H NMR (270MHz) ($CDCl_3$) δTMS 3.48 (2H, s); 3.84 (3H, s); 3.86 (3H, s); 6.52 (1H, d, J = 8.2Hz); 6.86 (1H, d, J = 8.2Hz); 7.75 (1H, br s, D_2O exch.).

IR (KBr) 3157, 1700, 1639, 1505, 1465, 1448, 1349, 1268, 1225, 1202, 1089, 1047, 980, 781 cm^{-1}.

microanalysis calc'd. for: C, 62.17; H, 5.74; N, 7.25; found: C, 62.38; H, 6.00 N, 7.11.

m.p.194–195°.

(lit. ref. 44, m.p. 200 °C, colorless leaflets, recrystallized from water)



120 **121**

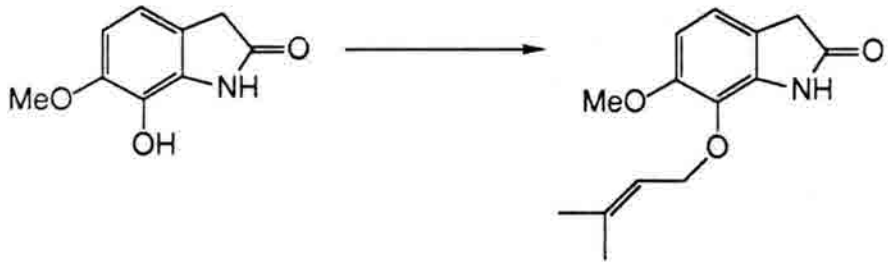
1,3-Dihydro-7-hydroxy-6-methoxy-2*H*-indol-2-one (121)

To a stirred cold (–78 °C) solution of **120** (40.4mg, 0.209mmol, 1.0eq) in CH_2Cl_2 (0.15mL) was added BBr_3 (0.251mL, 0.251mmol, 1.2eq, 1M/CH_2Cl_2). The resulting mixture was stirred under N_2 for 2 hours. The mixture was poured into ice/water (15mL) and stirred for 1 hour. This was subsequently extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to dryness. chromatography; PTLC, 5% CH_3OH/CH_2Cl_2, gave a pink–white solid. yield; 28.1mg, 75%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.57 (1H, s, D_2O exch.); 3.50 (2H, s); 3.89 (3H, s); 6.52 (1H, d, J = 8.0Hz); 6.73 (1H, d, J = 8.0Hz); 7.63 (1H, br s, D_2O exch.).

IR (neat) 3132, 1692, 1638, 1506, 1464, 1351, 1268, 1203, 1089, 1047, 980, 779 cm^{-1}.

MS (EI) 179: m/e (relative intensity) 180 (M^+, 12); 179 (100); 164 (4.3); 151 (14); 122 (39).



121 **122**

1,3-Dihydro-6-methoxy-7-[(3-methyl-2-butenyl)oxy]-2*H*-indol-2-one (122)

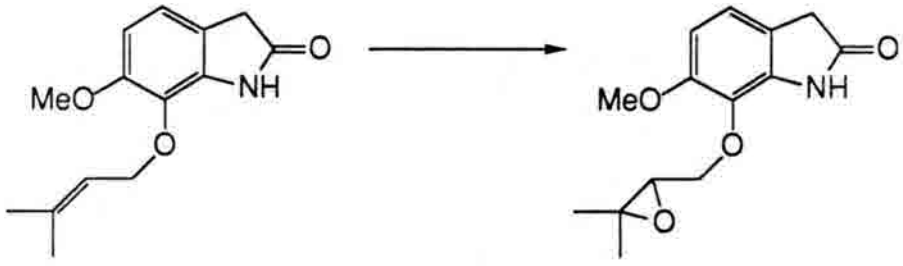
To a stirred cold (0 °C) solution of **121** (32.0mg, 0.179mmol, 1.0eq) in DMF (0.448mL) under Ar was added powdered K_2CO_3 (37.1mg, 0.268mmol, 1.5eq). After 10 minutes 1-bromo-3-methyl, 2-butene (0.23mL, 0.20mmol, 1.1eq) was added drop-

wise, with continued stirring for 20 hours (0 °C to r.t.). The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to dryness, togive a redish solid. yield; 36.9mg, 84%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.65 (3H, s); 1.76 (3H, s); 3.50 (2H, s); 3.86 (3H, s); 4.55 (2H, d, J = 7.4Hz); 5.44–5.49 (1H, m);6.53 (H, d, J = 8.1Hz); 6.87 (1H, d, J = 8.1Hz); 7.53 (1H, br s, D_2O exch.).

IR (neat) 3197, 2919, 1704, 1636, 1506, 1467, 1350, 1268, 1219, 1087, 971 cm^{-1}.

MS (EI) 247: m/e (relative intensity) 247 (0.7); 179 (59); 151 (10).



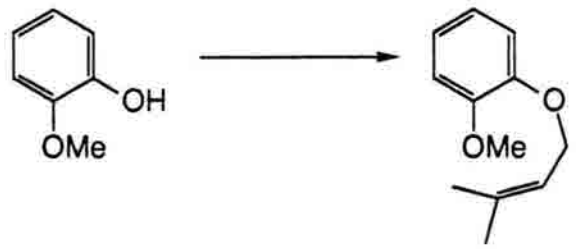
122 **123**

(±)-7-[(3,3-Dimethyloxiranyl)methoxy]–1,3-dihydro-6-methoxy-2*H*-indol-2-one (123)

To a stirred, cold (0 °C) solution of **122** (36.6mg, 0.148mmol, 1.0eq) in CH_2Cl_2 (0.5mL) was added m-CPBA (39.8mg, 0.192mmol, 1.3eq). After 2.5 hours the reaction mixture was poured into a separatory funnel washed three times with 5% $Na_2S_2O_3$ three times with 5% $NaHCO_3$ and once with brine. The solution was dried over $MgSO_4$ and reduced to dryness to give a redish solid. yield; 31.9mg, 82%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.27 (3H, s); 1.36 (3H, s); 3.1591H, dd, J = 4.4, 7.0Hz); 3.50 (2H, s); 3.85 (3H, s); 3.99 (1H, dd, J = 7.0, 11.5Hz); 4.37 (1H, dd, J = 4.4, 11.5Hz); 6.53 (1H, d, J = 8.1Hz); 6.90 (1H, d, J = 8.3Hz); 8.30 (1H, s, D_2O exch.)

IR (neat) 3204, 2967, 1736, 1708, 1640, 1504, 1464, 1340, 1272, 1204 cm^{-1}.



143

1-Methoxy-2-[(3-methyl-2-butenyl)oxy]-benzene (143)

To a stirred solution of K_2CO_3 (5.60g, 41.0mmol, 1.5 eq) in DMF (61.7mL) under N_2, at 0 °C was added 2-methoxyphenol (3.0mL, 27mmol, 1.0eq). After 10 minutes 1-bromo, 3-methylbut-2-ene (3.25mL, 30.0mmol, 1.1eq) was then added dropwise. The reaction was stirred 24h at room temperature, diluted with water and extracted with CH_2Cl_2. The organic layer was washed with NaOH (0.5M) brine, dried over $MgSO_4$, and concentrated to dryness to give a yellow–brown oil. yield; 3.27g, 62%

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.72 (3H, s); 1.76 (3H, s); 3.84 (2H, s); 4.56 (2H, d, J = 6.6Hz); 5.50–5.55 (1H, m); 6.84–6.90 (4H, m).

IR (neat) 2932, 1592, 1505, 1455, 1251, 1224, 1179, 1123, 1029, 1001, 741 cm^{-1}.

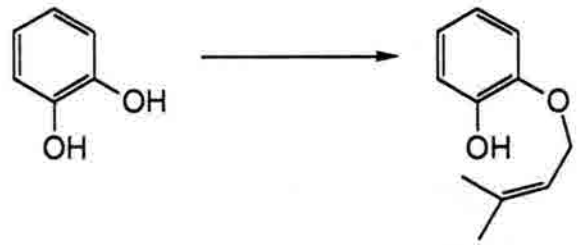
143 **144**

(±)-1-Methoxy-2-[(3,3-dimethyloxiranyl)methoxy]-benzene (144)

To a stirred solution of **143** (1.17g, 6.07mmol, 1.0eq)in CH_2Cl_2 (15mL) was added m-CPBA (2.28g, 13.2mmol, 1.7eq) at 0 °C, under N_2. After 2 hours the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with10% $Na_2S_2O_3$, sat. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated to dryness to give a brown oil. yield; 1.20g, 95%.

^{1}H NMR (300MHz) ($CDCl_3$) δ 1.30 (3H, s); 1.35 (3H, s); 3.16 (1H, t, J = 5.1Hz); 3.85 (3H, s); 4.10 (1H, dd, J = 5.3, 11.4Hz); 4.20 (1H, dd, J = 4.8, 11.4Hz); 6.85–6.97 (4H, m).

IR (neat) 2965, 2931, 1593, 1506, 1456, 1254, 1225, 1179, 1124, 1027, 744 cm^{-1}.



152

2-[(3-Methyl-2-butenyl)oxy]-phenol (152)

To a stirred, cold (0 °C) dark, solution of catechol (2.07g, 18.8mmol, 5.0eq) in DMF (65mL) flushed with Ar was added anhydrous K_2CO_3 (0.520g, 3.76mmol, 1.0eq). After 5 minutes, prenyl bromide (0.441mL, 3.76mmol, 1.0eq) was added dropwise. The reaction was kept at 0 °C for ≈ 6 hours and stirred at room temperature for an additional 18 hours. The mixture was then poured into a separatory funnel, diluted with H_2O (100mL) and extracted 5 times with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness . chromatography; (radial) 1% ethyl acetate/hexane, colorless oil. yield; 479mg, 71%. An analytical sample was obtained by PTLC; hexane.

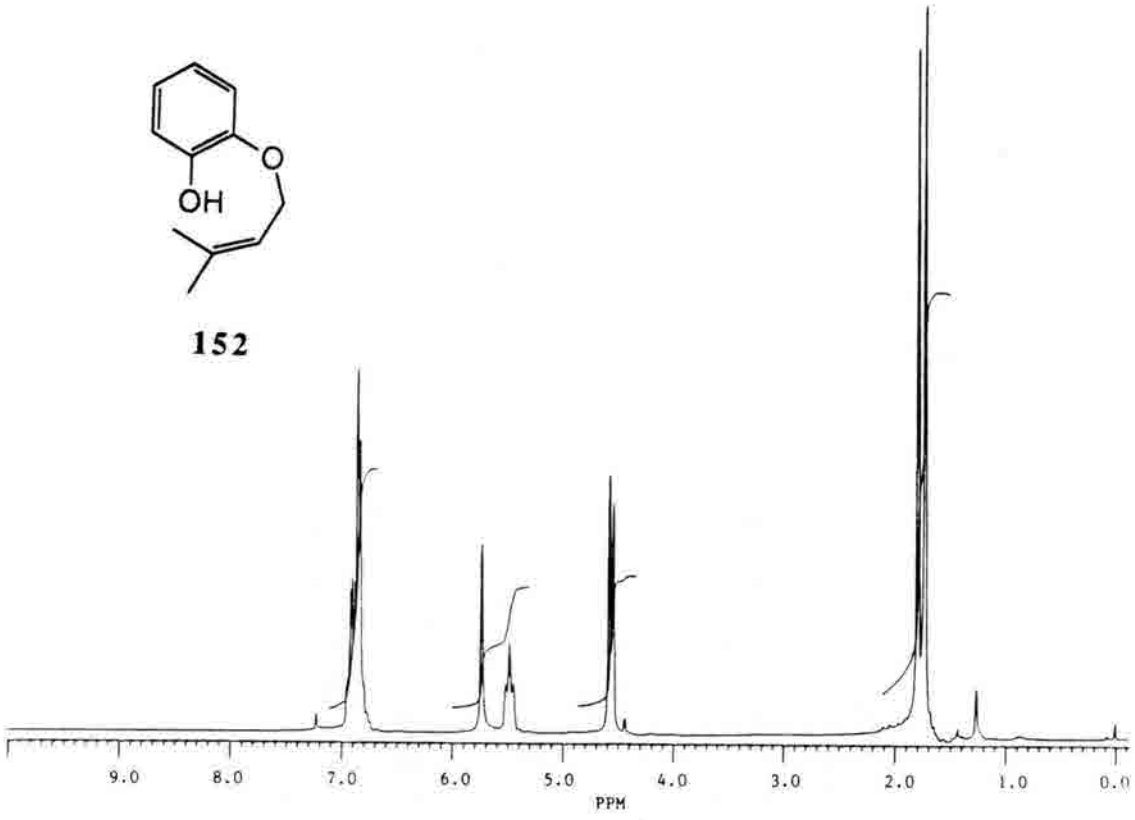
^{1}H NMR (300 MHz) ($CDCl_3$) δTMS 1.74 (3H, s); 1.80 (3H, s); 4.57 (1H, d, J = 6.8Hz); 5.49 (1H, m); 5.70 (1H, s, D_2O exch.); 6.82–6.92 (4H, m).

IR (NaCl, neat) 3533, 2932, 1612, 1502, 1467, 1385, 1259, 1221, 1106, 997, 743 cm^{-1}.

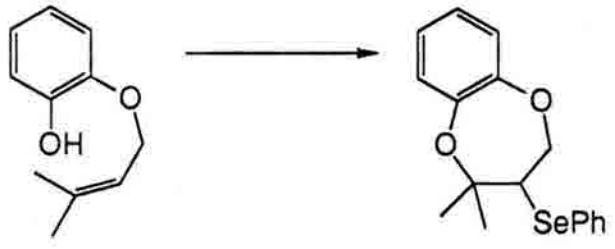
EI m/e 178 (relative intensity) 178 (11), 161 (11), 110 (78), 69 (67), 32 (100).

microanalysis calc'd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92 Found: C, 73.88; H, 8.00.

m.p. oil.



152



152 **153**

(±)-3,4-Dihydro-2,2-dimethyl-3-(phenylseleno)-2*H*-benzodioxepin (153)

A solution of N-PSP (134.0mg 0.4400mmol, 1.3eq), camphorsulfonic acid (cat amount) in acetonitrile (10mL) was slowly (25min.) added to a stirred solution of **152** (61.5mg, 0.340mmol, 1.0eq) in acetonitrile (2.5mL) at –23 °C, under N_2. The reaction was kept at –23 °C for 6 hours and stirred at room temperature for 14 more hours. The reaction mixture was poured into a separatory funnel, diluted with ether, washed with 1M NaOH. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. chromatography; (radial) 1:20 ethyl acetate/hexane, yield; 3mg, 3%.

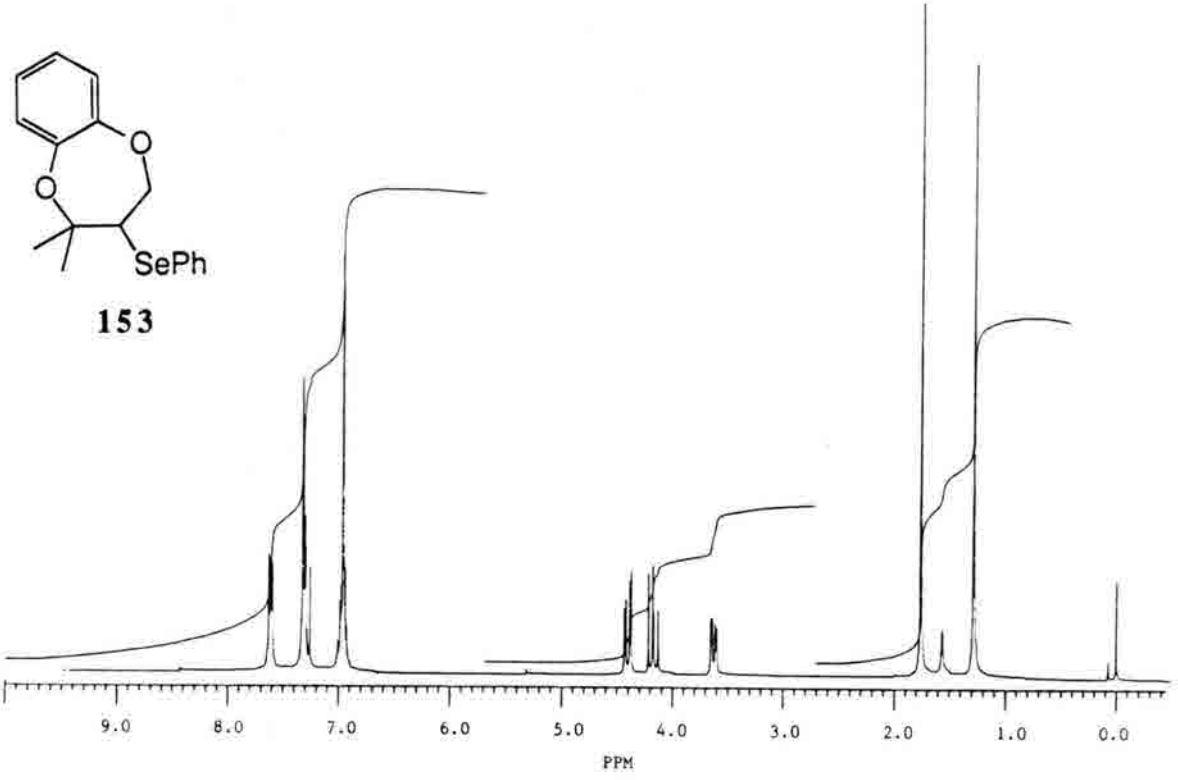
A solution of phenylselenochloride (117.8mg, 0.6150mmol, 1.05eq) in ethyl acetate (4.1mL, 0.15M) was slowly (1mmol/hour) added to a stirred solution of **153** (104.4mg, 0.5860mmol, 1.0eq) in ethyl acetate (3.90mL, 0.15m) at –75 °C under Ar. This mixture was allowed to reach room temperature, and stirred for a total of 17 hours. The solution was poured into a separatory funnel, washed twice with H_2O, and once with brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. chromatography; PTLC, 1:3 hexane/benzene, yield; 62.1mg, 32%. An analytical sample was obtained by PTLC; hexane, and then distilled under reduced pressure.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.28 (3H, s); 1.76 (3H, s); 3.62 (1H, dd, J = 3.4, 10.3Hz); 4.17 (1H, dd, J = 10.3, 12.6Hz); 4.40 (1H, dd, J = 3.5, 12.6Hz); 6.94–6.98 (4H, m); 7.30–7.34 (3H, m); 7.59–7.62 (2H, m).

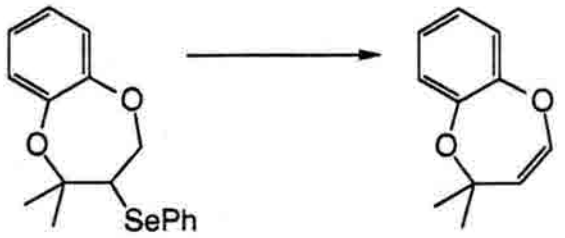
IR (NaCl, neat) 2986, 1491, 1256, 1088, 1000 cm^{-1}.

EI HRMS m/e 334.0473 ($C_{17}H_{18}O_2Se$ requires 334.0472).

m.p. oil.



153



153 **154**

2,2-Dimethyl-2*H*-1,5-benzodioxepin (154)

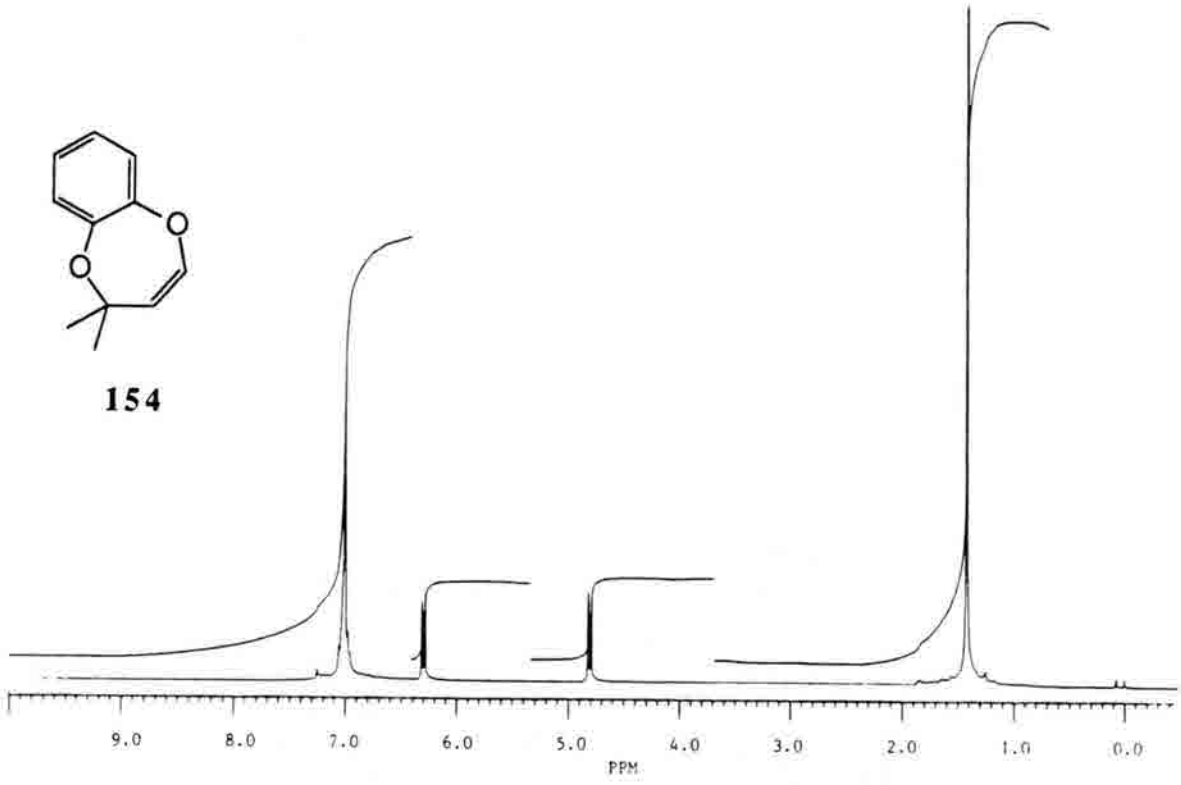
To a stirred solution of **153** (61.7mg, 0.185mmol, 1.0eq) in THF (3mL) was added H_2O_2 (0.21mL, 0.5mmol, 10eq) at 0 °C. The resulting solution was stirred for 0.5 hour and then refluxed 0.5 hour. The mixture was then poured into a separatory funnel, diluted with water and extracted with ether. The ethereal solution was washed with brine, dried over $MgSO_4$. and evaporated to dryness. chromatography; PTLC, 1:3 hexanes/ethyl acetate, pale yellow oil. yield; 16.0mg, 49%.

^{1}H NMR (300 MHz) ($CDCl_3$) δTMS 1.42 (6H, s); 4.81 (1H, d, J = 7.8Hz); 6.30 (1H, d, J = 7.8Hz); 6.95–7.06 (4H, m).

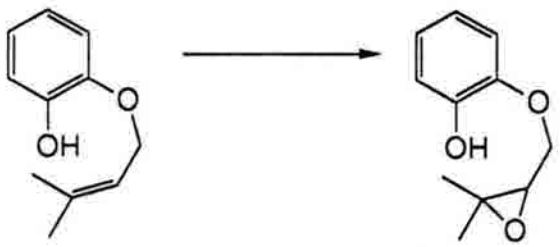
IR (neat) 2978, 1654, 1587, 1495, 1311, 1242, 750 cm^{-1}.

EI HRMS m/e 176.0835 ($C_{11}H_{12}O_2$ requires 176.0837).

m.p. oil.



154



152 **155**

(±)-2-[(3,3-Dimethyloxiranyl)methoxy]-phenol (155)

To a solution of **152** (1.31g, 7.35mmol, 1.0eq) in CH_2Cl_2 (40.0mL) under N_2, at 0 °C was added $NaHCO_3$ (803mg, 9.56mmol, 1.3eq) followed by m-CPBA (1.27g, 7.35mmol, 1.0eq). After 1.5 hours an additional amount of $NaHCO_3$ (812mg, 9.66mmol, 1.21eq) and m-CPBA (1.26g, 7.35mmol, 0.99eq) were added. This mixture was kept stirring at 0 °C for 2 more hours, when more $NaHCO_3$ (778mg, 9.27mmol, 1.3eq) and m-CPBA (1.12g, 6.49mmol, 0.88mmol) were added. After 2 more hours the cold mixture was filtered to remove the solids. The filtrate was washed 3 times with 10% $Na_2S_2O_3$,

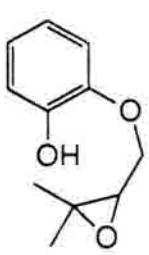
three times with brine, dried over $MgSO_4$ and evaporated to dryness. yield; 1.41g, 99%. An analytical sample was recrystallized from toluene to give a glassy solid.

^1H NMR (270 MHz) ($CDCl_3$) δTMS 1.37 (3H, s); 1.41 (3H, s); 3.18 (1H, dd, J = 4.2, 6.3Hz); 4.07 (1H, dd, J = 6.4, 11.0Hz); 4.28 (1H, dd, J = 4.2, 11.0Hz); 5.78 (1H, s, D_2O exch.); 6.81–6.97 (4H, m).

IR (NaCl, neat) 3413, 2966, 1590, 1502, 1267, 744 cm^{-1}.

microanalysis calc'd. for $C_{11}H_{13}O_4$: C, 68.02; H, 7.26 Found: C, 67.91; H, 7.39.

m.p. 36–37 °C.



155

155 **148**

(±)-3,4-Dihydro-2,2-dimethyl-2*H*-1,5-benzodioxepin-3-ol (148)

A flame dried flask, flushed with argon was charged with dry THF (85.4mL, 0.085mmol). Tin tetrachloride (0.85mL, 7.3mmol, 1.0eq) was then added dropwise in 5 min. After 10 minutes a solution of **155** (1.41g, 7.26mmol, 1.0eq) in dry THF (13.8mL) was added slowly (dropwise) to the mixture. The reaction mixture was stirred at room temperature for 20 additional minutes. It was then poured into saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$ and evaporated to dryness. chromatography; (radial) 1:7 ethyl acetate/hexanes, yield; 842mg, 60% or 59% for two steps. An analytical sample was obtained by PTLC; 5:1 ethyl acetate/hexane, and then distillation under reduced pressure.

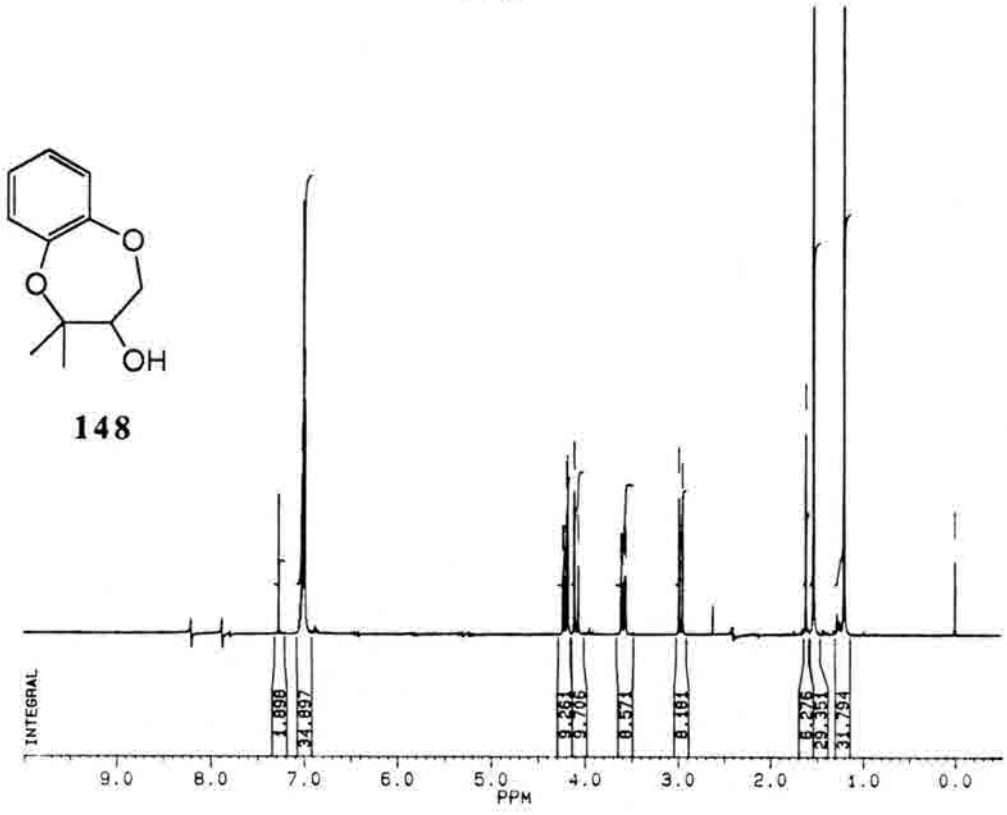
^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.20 (3H, s); 1.53 (3H, s); 2.96 (1H, d, J = 11.3Hz , D_2O exch.); 3.58 (1H, ddd, J = 1.1, 4.0, 11.3Hz); 4.08 (1H, dd, J = 1.1, 12.6Hz); 4.20 (1H, dd, J = 4.0, 12.6Hz); 6.98–7.02 (4H, m).

IR (NaCl, neat) 3448, 2978, 1596, 1490, 1261 cm^{-1}.

EI m/e 194 (relative intensity) 194 (41), 176 (19), 136 (57), 121 (100), 59 (63).

EI HRMS m/e 194.0943 ($C_{11}H_{14}O_3$ requires 194.0943).

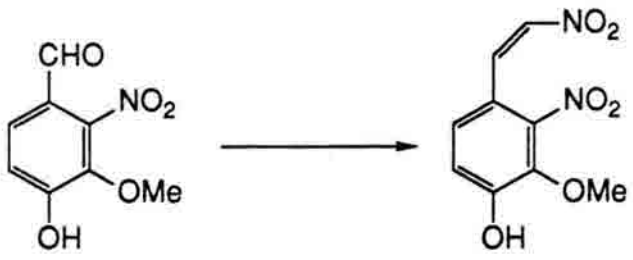
m.p. oil.



148 **154**

2,2-Dimethyl-2*H*-1,5-benzodioxepin (154)

To a solution of the **148** (76.2mg, 0.392mmol, 1.0eq) in HMPA (2mL) under N_2 at room temperature was added MTPI (291.5mg, 0.644mmol, 1.6eq) all at once. After stirring for 1 day the mixture was poured into a separatory funnel containing 1 M NaOH. It was then extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation gave a crude yield of 163.5mg. chromatography; (radial)1:10 ethyl acetate/hexanes, 1:5 ethyl acetate/hexanes yield; 46mg, 66%.



131 **158**

4-Hydroxy-3-methoxy-2-nitro-β-nitrostrene (158)

To a flask charged with **131** (9.00g, 45.4mmol, 1.0eq) and ammonium acetate (4.20g, 54.5mmol, 1.2eq) was added acetic acid (300mL) and nitromethane (6.15mL, 114mmol, 2.5eq). This mixture was gently refluxed for 8 hours and then cooled in an ice bath. The mixture was poured into a separatory funnel, and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated to dryness. chromatography; column, 3:2 hexane/ethyl acetate, yield; 7.60g, 88%. An analytical sample was recrystallized from $EtOH/H_2O$ to give bright yellow flakes.

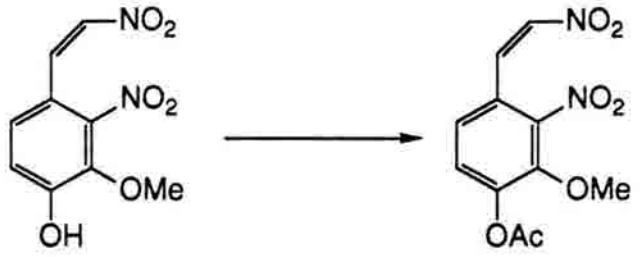
^1H NMR (270MHz) (DMSO-D_6) δTMS 3.87 (3H, s); 5.76 (1H, s, D_2O exch.); 7.13 (1H, d, J = 8.8Hz); 7.58 (1H, d, J = 13.3Hz); 7.77 (1H, d, J = 8.8Hz); 8.14 (1H, d, J = 13.4Hz).

IR (KBr) 3435 (br), 1574, 1518, 1355, 1319, 1288, 1248, 1147, 1031, 830, 814 cm^{-1}.

microanalysis calc'd. for $C_9H_8N_2O_6$ C, 45.01; H, 3.36; N, 11.66; found: C, 44.86, H, 3.50; N, 11.42.

m.p. 192–193 °C.

(lit. ref. 68b, m.p. 140-141 °C, bright yellow prisms, recrystallized from 50% acetic acid).



158 **159**

4-Acetoxy-3-methoxy-2-nitro-β-nitrostyrene (159)

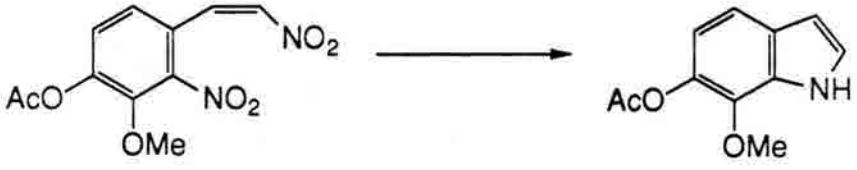
A flask containing **158** (544.7mg, 2.267mmol, 1.0eq) and acetic anhydride (5.2mL) was gently refluxed for 2 hours. The solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to dryness. crude yield; 682.1mg, recrystallized, ethanol/water to give a bright yellow crystalline solid.. yield; 407.8mg, 63%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 2.40 (3H, s); 3.23 (3H, s); 7.36 (1H, s); 7.37 (1H, s); 7.48 (1H, d, J = 13.5Hz); 7.86 (1H, d, J = 13.5Hz).

IR (neat) 1671, 1598, 1581, 1539, 1510, 1372, 1318, 1276, 1202, 1041, 828 cm^{-1}.

m.p. 137–138 °C

(lit. ref. 68a, m.p. 101-102 °C, bright yellow solid, recrystallized from dilute alcohol).



159 **160**

6-Acetoxy-7-methoxy-1*H*-indole (160)

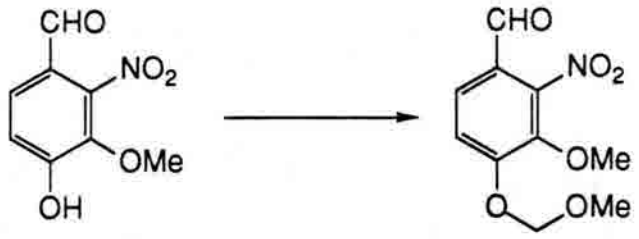
To a stirred solution of **159** (68.8mg, 0.244mmol, 1.0eq) in ethanol (0.87mL) and acetic acid (0.87mL) was added iron powder (248mg). This was refluxed for 15 minutes until the pale yellow solution turned dark brown. The mixture was filtered, diluted with water and extracted with diethyl ether. The organic layer was washed with 5% $NaHCO_3$,

brine, dried over $MgSO_4$ and concentrated to dryness. chromatography; PTLC, 5% methanol, 3:2 hexane/ethyl acetate,(tan waxy crystals). yield; 22.9mg, 46%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 2.30 (3H, s); 3.83 (3H, s); 6.40–6.42 (1H, m); 6.77 (1H, d, J = 8.4Hz); 6.93–6.95 (1H, m); 7.26 (1H, d, J = 8.5Hz); 8.69 (1H, s, D_2O exch.).

IR (neat) 3372 (br) 1754, 1586, 1502, 1446, 1370, 1341, 1238, 1207, 1159, 1058, 1024, 672 cm^{-1}.

(lit. ref. 68a, m.p. 81 °C, colorless plates, recrystallized from light petroleum).



131 **163**

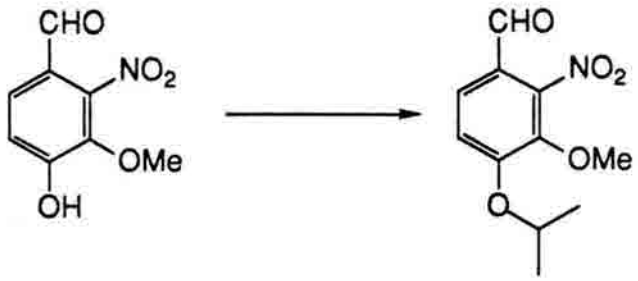
3-Methoxy-4-[(methoxymethyl)oxy]-2-nitro-benzaldehyde (163)

To a stirred solution of **131** (102.8mg, 0.5188mmol, 1.0eq) in THF (1.5mL) at 0 °C under Ar was added NaH (28.3mg, 0.57mmol, 1.1eq). This was followed 5 minutes later by methyl chloromethyl ether (0.059mL, 0.78mmol, 1.5eq). The resulting solution was stirred for 18 hours while reaching room temperature during this time. The solution was diluted with ethyl acetate, washed three times with 1M NaOH, brine and dried over $MgSO_4$. After solvent removal a spectrally pure yellow oil was obtained. yield; 117.2mg, 93%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.54 (3H, s); 3.97 (3H, s); 5.49 (2H, s); 7.40 (1H, d, J = 8.1Hz); 7.64 (1H, d, J = 8.1Hz); 9.89 (1H, s).

IR (neat) 2923, 1697, 1600, 1545, 1500, 1458, 1373, 1278, 1150, 1003, 890 cm^{-1}.

MS (EI) 241: m/e (relative intensity) 241 (0.5); 95 (10); 57 (16); 45 (60); 28 (100).



131 **164**

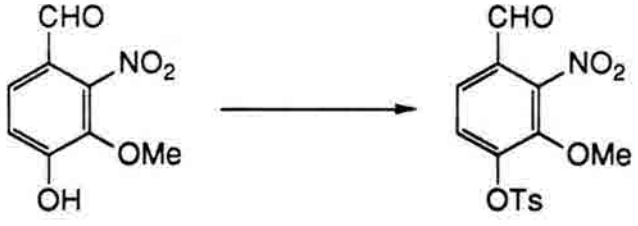
4-Isopropoxy-3-methoxy-2-nitro-benzaldehyde (164)

To a stirred solution of **131** (1.008g, 5.087mmol, 1.0eq) in DMF (10.0mL) was added K_2CO_3 (1.406g, 10.17mmol, 2.0eq) followed by isopropyl bromide (0.53mL, 5.6mmol, 1.1eq). The solution was then heated to 100 °C, and stirred for 2 days. The resulting solution was poured into water, extracted with methylene chloride, washed with brine and dried over $MgSO_4$. After solvent removal the spectrally pure product was obtained (brown solid). yield; 1.20g, 98%.

^{1}H NMR (270MHz) ($CDCl_3$) δTMS 1.46 (6H, d, J = 6.0Hz); 3.94 (3H, s); 4.80 (1H, septet); 7.14 (1H, d, J = 8.7Hz); 7.63 (1H, d, J = 8.7Hz); 9.78 (1H, s).

IR (neat) 1697, 1600, 1549, 1497, 1462, 1374, 1282, 1108, cm^{-1}.

MS (EI) 239: m/e (relative intensity) 239 (7); 197 (10); 152 (18); 121 (26); 93 (29); 28 (100).



131 **165**

3-Methoxy-2-nitro-4-[(toluenesulfonyl)oxy]-benzaldehyde (165)

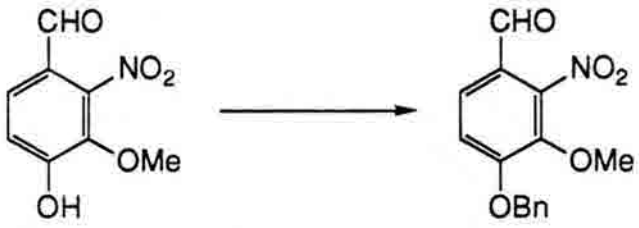
To a stirred solution of **131** (141.1mg, 0.7172mg, 1.0eq) in acetone (2.8mL) was added K_2CO_3 (148.7mg, 1.076mmol, 1.5eq) followed immediately by toluenesulfonyl chloride (150.4mg, 0.7889mmol, 1.1eq). The resulting mixture was kept

stirring for 4.5 hours. This was then extracted with ethyl acetate, washed with water, brine and dried over $MgSO_4$. After solvent removal the product was obtained (orange crystals). yield; 272.1mg, 100%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 2.48 (3H, s); 3.84 (3H, s); 7.39 (2H, d, J = 8.1Hz); 7.56 (1H, d, J = 8.6Hz); 7.69 (1H, d, J = 8.5Hz); 7.79 (2H, d, J =8.4Hz); 9.86 (1H, s).

IR (neat) 1708, 1600, 1549, 1487, 1380, 1272, 1180, 1092, 969, 826, 739 cm^{-1}.

MS (EI) 351: m/e (relative intensity) 351 (1); 190 (9); 155 (7); 91 (100); 28 (100).



131 **166**

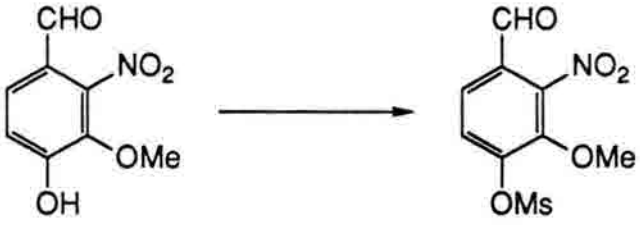
4-Benzyloxy-3-methoxy-2-nitro-benzaldehyde (166)

To a stirred solution of **131** (106.9mg, 0.5422mmol, 1.oeq) in DMF (1.1mL) at 0 °C was added K_2CO_3 (75mg, 0.54mmol, 1.0eq) followed by benzylbromide (0.071mL, 0.60mmol, 1.1eq). The resulting solution was stirred 1.5h, diluted with water, extracted with methylene chloride, washed with brine and dried over $MgSO_4$. After solvent removal, the product was obtained (yellow solid). yield; 162.6mg, 100%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.95 (3H, s); 5.26 (2H, s); 7.18 (1H, d, J = 8.6Hz); 7.39–7.44 (5H, m); 7.60 (1H, d, J = 8.4Hz); 9.76 (1H, s).

IR (neat) 1697, 1600, 1544, 1503, 1456, 1380, 1272, 1205, 1072, 1015, 959, 903, 749 cm^{-1}.

MS (EI) 287: m/e (relative intensity) 287 (1); 91 (100); 65 (37); 28 (100).



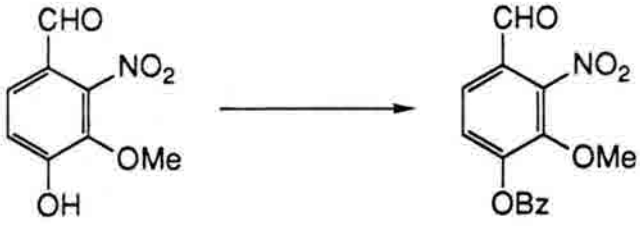
131 **167**

4-[(Methanesulfonyl)oxy]-3-methoxy-2-nitro-benzaldehyde (167)

To a stirred solution of **131** (143.8mg, 0.7294mmol, 1.0eq) at 0 °C in pyridine (1.4mL) under Ar, was added methanesulfonylchloride (0.12mL, 1.60mmol, 2.2eq) in two portions. After two hours the reaction mixture was poured into 11mL of 2M HCl and stirred at 0 °C for 0.5 hours. It was then extracted with ethyl acetate, washed with water, 1M NaOH, brine and dried over $MgSO_4$. The resulting solution was evaporated to give the desired product (orange solid). yield; 106.0mg, 53%.

^{1}H NMR (270MHz) ($CDCl_3$) δTMS 3.30 (3H, s); 4.05 (3H, s); 7.70 (1H, d, J = 8.6Hz); 7.77 (1H, d, J = 8.4Hz); 9.92 (1H, s).

IR (neat) 1703, 1545, 1487, 1374, 1272, 1180, 1164, 964, 841, 831, 790 cm^{-1}.



131 **168**

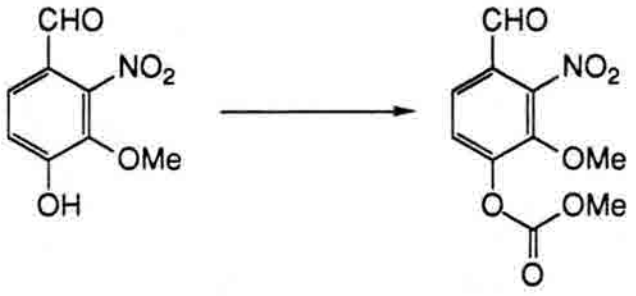
4-Benzoyloxy-3-methoxy-2-nitro-benzaldehyde (168)

To a stirred solution of **131** (209.2mg, 1.056mmol, 1.0eq) in dioxane (2.0mL) was added pyridine (0.12mL, 1.2mmol, 1.1eq) followed by benzoyl chloride (0.12mL, 1.2mmol, 1.1eq). The resulting solution was refluxed for 2.5 hours, poured into a separatory funnel diluted with water and extracted with ethyl acetate. The organic layer was washed with water, sodium bicarbonate, dilute HCl, brine and then dried over

$MgSO_4$. The resulting solution was evaporated to give the desired product (tan solid). yield; 317.2mg, 100%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.96 (3H, s); 7.54–7.60 (3H, m); 7.69–7.77 (2H, m); 8.20–8.23 (2H, m); 9.92 (1H, s).

IR (neat) 1749, 1708, 1600, 1549, 1487, 1456, 1369, 1262, 1231, 1200, 1174, 1051, 1020, 703 cm^{-1}.



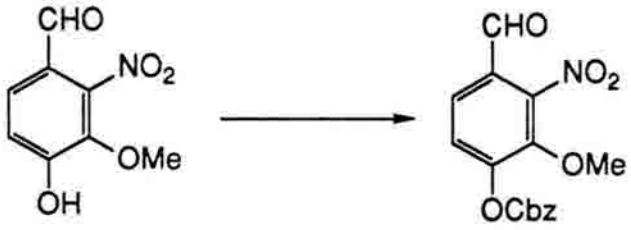
131 **169**

4-[(Carbomethoxy)oxy]-3-methoxy-2-nitro-benzaldehyde (169)

To a stirred solution of **131** (104.5mg, 0.5270mmol, 1.0eq) in DMF (1.0mL) at 0 °C was added K_2CO_3 (50.3mg, 0.364mmol, 0.69eq). After 15 minutes methyl chloroformate (0.045mL, 0.58mmol, 1.1eq) was syringed into the flask. The solution was stirred under argon for 24hours (0 °C to r.t.). It was then poured into water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated to dryness. chromatography; radial, 3:2 ethyl acetate/ hexane, (brown crystalline solid) yield 50%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.98 (6H, s); 7.56 (1H, d, J = 8.5Hz); 7.73 (1H, d, J = 8.5Hz); 9.90 (1H, s).

IR (neat) 1774, 1708, 1600, 1549, 1492, 1462, 1441, 1369, 1267, 1231, 1200, 964, 928, 815 cm^{-1}.



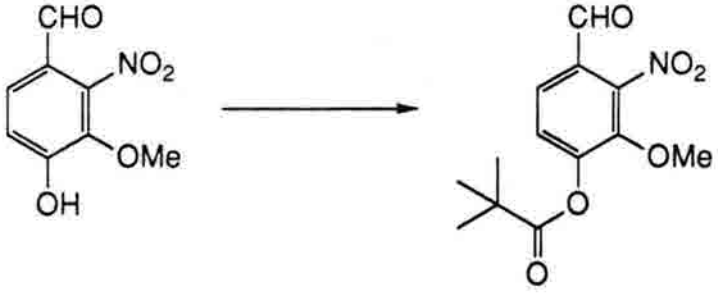
131 **170**

4-[(Carbobenzoxy)oxy]-3-methoxy-2-nitro-benzaldehyde (170)

To a stirred solution of **131** (121.0mg, 0.6106mmol, 1.oeq) in THF (1.0mL) was added benzyl chloroformate (0.096mL, 0.672mmol, 1.1eq) at 0 °C under Ar. After 15 minutes pyridine (0.068mL, 0.672mmol, 1.1eq) was added and stirred for 24 more hours (0 °C to r.t.). The solution was acidified, HCl (10.0mL, 2M), diluted with water (20mL) and extracted with methylene chloride. The organic layer was washed with brine and dried over $MgSO_4$, and concentrated to dryness. chromatography; radial, 3:2 hexane/ethyl acetate, (brown oil). yield; 143.3mg, 71%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.88 (3H, s); 5.30 (2H, s); 7.38–7.40 (5H, m); 7.52 (1H, d, J = 8.5Hz); 7.65 (1H, d, J = 8.4Hz); 9.83 (1H, s).

IR (neat) 1774, 1701, 1600, 1549, 1492, 1456, 1426, 1374, 1262, 1220, 1195, 959, 749, 697 cm^{-1}.



131 **171**

3-Methoxy-2-nitro-4-[(pivaloyl)oxy]-benzaldehyde (171)

To a stirred solution of **131** (214.3mg, 1.08mmol, 1.oeq) under argon at 0 °C in pyridine (2.2mL) was added pivaloyl chloride (0.27mL, 2.16mmol, 2.0eq). The solution was allowed to come to room temperature. After six days, it was poured into water,

extracted with ethyl acetate, washed with $CuSO_4$, brine, dried over $MgSO_4$, and concentrated to dryness. chromatography; radial, 3:2 hexane/ethyl acetate, (brown oil). yield, 126.9mg, 45%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.41 (9H, s); 3.93 (3H, s); 7.41 (1H, d, J = 8.5Hz); 7.72 (1H, d, J = 8.5Hz); 9.89 (1H, s).

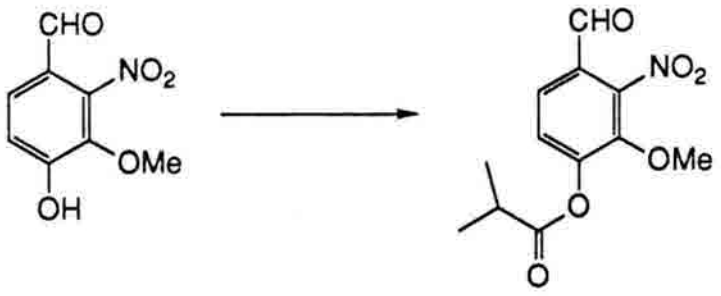
131 **172**

3-Methoxy-2-nitro-4-benzaldehyde (172)

To a stirred solution of **131** (114.0mg, 0.5782mmol, 1.0eq) in THF (0.9mL) at 0 °C under argon was added pyridine (0.120mL, 1.16mmol, 2.0eq). After 5 minutes phenyl chloroformate (0.14mL, 1.16mmol, 2.0eq) was added. In two hours the reaction mixture solidified so more THF (2mL) was added at room temperature. The mixture was allowed to stir two additional hours when an another portion of THF (2mL) and water (1mL) were added to the reaction flask. This was stirred a final 15 minutes. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, $CuSO_4$, brine, dried over $MgSO_4$, and concentrated to dryness, (whitish solid). crude yield; 198.0mg chromatography; radial, 1:4 ethyl acetate/hexane yield; 48.6mg, 34%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 4.05 (3H, s); 7.25–7.34 (3H, m); 7.41–7.47 (2H, m); 7.64 (1H, d, J = 8.5Hz); 7.73 (1H, d, J = 8.5Hz); 9.90 (1H, s).

IR (neat) 1780, 1708, 1549, 1492, 1282, 1251, 1221, 1185, 1169 cm^{-1}.



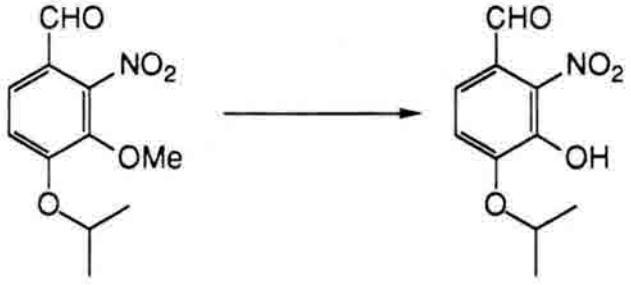
131 **173**

4-[Carboisopropyl)oxy]-3-methoxy-2-nitro-benzaldehyde (173)

A stirred solution of **131** (61.9mg, 0.314mmol, 1,0eq) in isobutyric anhydride (1.0mL, 6.03mmol, 19.2eq) and pyridine (0.03mL, 0.314mmol, 1.0eq) under Ar was slowly heated to 100 °C for 3.5 hours. The mixture was then poured into water, extracted with ethyl acetate, washed with brine and dried over $MgSO_4$, and concentrated to dryness. chromatography; PTLC, 1:3 ethyl acetate/hexane, (brown oil). yield; 55.7mg, 66%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.37 (6H, d, J = 6.9Hz); 2.92 (1H, septet); 7.44 (1H, d, J = 8.4Hz); 9.90 (1H, s).

IR (neat) 1769, 1708, 1600, 1549, 1492, 1462, 1369, 1277, 1108, 1082 cm^{-1}.



164 **174**

3-Hydroxy-4-isopropoxy-2-nitro-benzaldehyde (174)

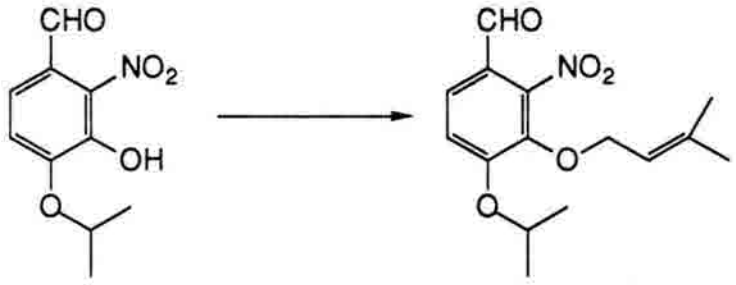
A stirred solution of **164** (167.3mg, 0.6964mmol, 1.0eq) and lithium chloride (118.1mg, 2.78mmol, 4.0eq) in DMF (1.4mL) was slowly heated to 100–105 °C for 24 hours. The mixture was cooled, poured into 1M NaOH and washed with methylene chloride. The methylene chloride solution was discarded and the water layer acidified and

extracted with ethyl acetate. The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated to dryness, (dark brown oil). yield; 143.2mg, 91%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.47 (6H, d, J = 8.1Hz); 4.78 (1H, septet); 7.10 (1H, d, J = 13.5Hz); 7.44 (1H, d, J = 10.8Hz); 9.90 (1H, s).

IR (neat) 3368 (br), 1622, 1551, 1496,1469, 1262, 1207, 1115 cm^{-1}

MS (EI) 225: m/e (relative intensity) 225 (1); 183 (2); 137 (6); 120 (4); 73 (79); 28 (100).



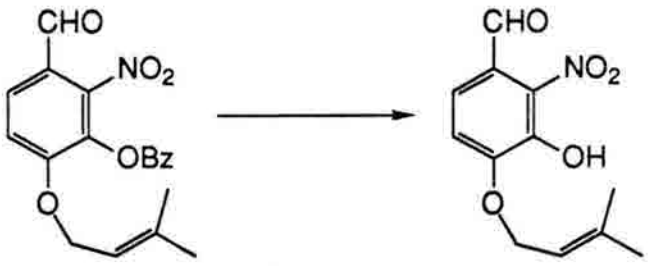
174 **180**

4-Isopropoxy-3-[(3-methyl-2-butenyl)oxy]-2-nitro-benzaldehyde (180

To a stirred solution of **174** (140.1mg, 0.6193mmol, 1.0eq) in DMF (10.0mL) at 0 °C, under Ar was added K_2CO_3 (171.2mg, 1.239mmol, 1.5eq) and prenyl bromide (0.145mL, 1.239mmol, 2.0eq). The resulting solution was stirred for 1 hour. It was then poured into water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and evaporated to give a brown oil. yield; 183.3mg, 100%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.46 (6H, d, J = 6.2Hz); 1.70 (3H, s); 1.76 (3H, s); 4.63 (2H, d, J = 7.6Hz); 4.79 (1H, septet); 5.41–5.48 (1H, m); 7.13 (1H, d, J = 8.7Hz); 7.62 (1H, d, J = 8.7Hz); 9.76 (1H, s).

IR (neat) 1698, 1600, 1545, 1496, 1284, 1104 cm^{-1}.



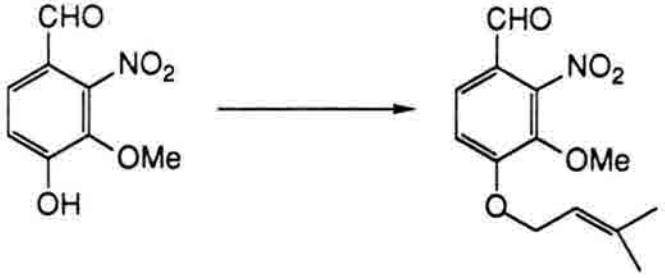
183 **184**

3-Hydroxy-4-[(3-methyl-2-butenyl)oxy]-2-nitro-benzaldehyde (184)

A solution of **183** (11.5mg, 0.0324mmol, 1.0eq) was stirred with NaOH (0.5mL, 1M) and dioxane (0.5mL) for 14.5 hours at room temperature. It was and then refluxed for 50 minutes with an additional amount of NaOH (0.5mL) and dioxane (0.5mL). The reaction mixture was acidified (HCl) and extracted with ethyl acetate. The organic layer was washed with dilute $NaHCO_3$, brine, dried over $MgSO_4$ and evaporated. chromatography; PTLC, 1:1 hexane/ethyl acetate, (brown powder). yield; 3.0mg, 37%.

^1H NMR (300MHz) ($CDCl_3$) δ 1.75 (3H, s); 1.79 (3H, s); 4.70 (2H, d, J = 6.9Hz); 5.43–5.48 (1H, m); 7.07 (1H, d, J = 8.4 Hz); 7.42 (1H, d, J = 8.5Hz); 8.33 (1H, br s, D_2O exch.); 9.99 (1H, s).

IR (neat) 3373 (br) 1690, 1613, 1544, 1504, 1479, 1376, 1283, 1196, 1059, 1006, 910, 813, 766 cm^{-1}.



131 **185**

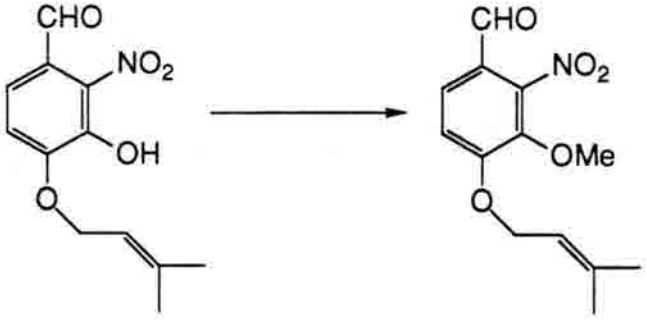
3-Methoxy-4-[(3-methyl-2-butenyl)oxy]-2-nitro-benzaldehyde (185)

To a stirred solution of **131** (45.0mg, 0.227mmol, 1.0eq) in DMF (0.5mL) at 0 °C under argon was added K_2CO_3 (31.4mg, 0.227mmol, 1.0eq) followed by prenyl bromide

(0.032mL, 0.273mmol, 1.2eq). After 20 minutes, the reaction mixture was allowed to reach room temperature, and stirred an additional 19 hours. The mixture was diluted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, and concentrated to dryness, (yellow solid). yield; 57.6mg, 100%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.78 (3H, s); 1.82 (3H, s); 3.93 (3H, s); 4.72 (2H, d, J = 6.6Hz); 5.46–5.50 (1H, br m); 7.12 (1H, d, J = 8.6Hz); 7.62 (1H, d, 8.7Hz); 9.77 (1H, s).

IR (neat) 1695, 1601, 1546, 1502, 1458, 1376, 1282, 1210, 1012 cm^{-1}.



184 **185**

3-Methoxy-4-[(3-methyl-2-butenyl)oxy]-2-nitro-benzaldehyde (185)

To a stirred solution of **184** (23.2mg, 0.0923mmol, 1.0eq) in acetone (0.5mL) was added K_2CO_3 (7.5mg, 0.054mmol, 0.59eq) and methyl iodide (0.009mL, 0.1385mmol, 1.5eq). The reaction mixture was gently refluxed for 24 hours, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and reduced to dryness. chromatography; PTLC, 3:2 hexane/ethyl acetate, (yellow solid). yield 10.0mg, 41%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.78 (3H, s); 1.82 (3H, s); 3.95 (3H, s); 4.71 (2H, d, J = 6.7Hz); 5.45–5.50 (1H, br m); 7.10 (1H, d, J = 8.7Hz); 7.63 (1H, d, J = 8.7Hz); 9.79 (1H, s).

IR (neat) 1698, 1600, 1545, 1502, 1458, 1371, 1284, 1213, 1017 cm^{-1}.

131 **186**

3,4-Dihydroxy-2-nitro-benzaldehyde (186)

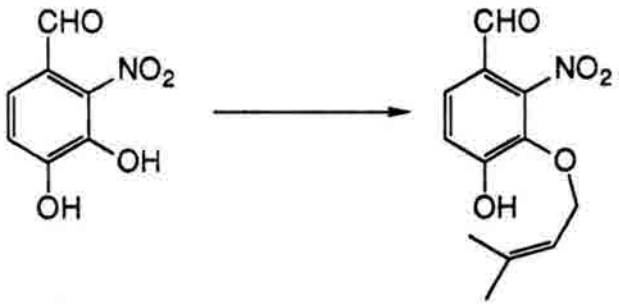
To a stirred solution of **131** (4.01g, 20.3mmol, 1.0eq) in CH_2Cl_2 (30mL) at –78 °C under N_2 was added dropwise, BBr_3 (51mL, 51mmol, 2.5eq). After 6 hours, it was placed in a freezer (–29 °C) for 12 hours. The reaction mixture was then poured into a beaker containing ice/water and stirred for 0.5 hours until the ice melted. The mixture was then poured into a large separatory funnel and extracted with ethyl acetate. The organic layer was washed and dried with brine and $MgSO_4$, rotoevaporation left a crude solid. re-crystallization; H_2O, yield; 3.36g, 92%. An analytical sample was recrystallized from toluene to give a yellow crystalline solid.

^1H NMR (300 MHz) (DMSO-D_6) δTMS 3.0–5.0 (2H, br s, D_2O exch.); 7.09 (1H, d, J = 8.3Hz); 7.42 (1H, d, J = 8.3Hz); 9.68 (1H, s).

IR (KBr) 3315 (br), 1671, 1614, 1540, 1376, 1298 cm^{-1}.

microanalysis calc'd. for $C_7H_5NO_5$: C, 45.91; H, 2.75; N, 7.65 Found: C, 46.06; H, 2.65; N, 7.43.

m.p. 177–178 °C.



186 **181**

4-Hydroxy-3-[(3-methyl-2-butenyl)oxy]-2-nitro-benzaldehyde (181)

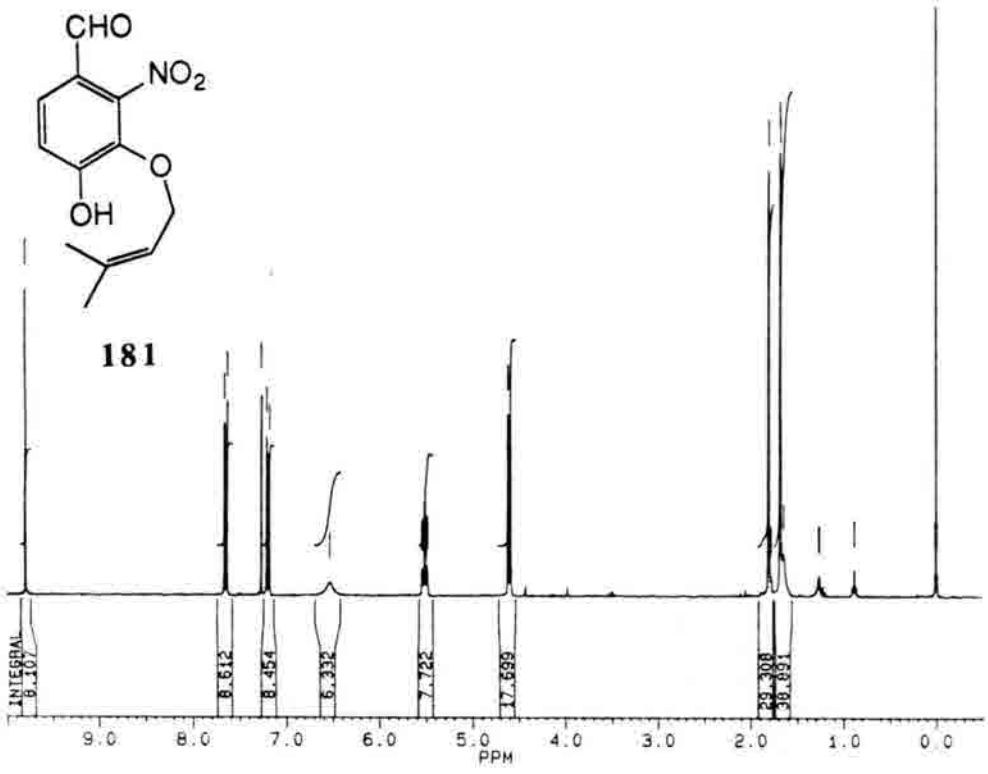
To a stirred solution of **186** (1.09g, 5.95mmol, 1.0eq) in DMF (12mL) at 0 °C under argon was added $NaHCO_3$ (500mg, 5.95mmol, 1.0eq). After 10 minutes an additional amount of $NaHCO_3$ (250mg, 2.98mmol, 0.5eq) was added. This mixture was stirred 10 minutes when prenyl bromide (0.77mL, 6.5mmol, 1.1eq) was added dropwise and allowed to reach room temperature. After 4 days K_2CO_3 (205mg, 1.49mmol, 0.25eq) was added plus an additional amount of prenyl bromide (0.14mL, 1.2mmol, 0.25eq). It was stirred one more day. The mixture was then diluted with H_2O and extracted with ethyl acetate. The resulting dark crude mixture was run through a plug of silica gel. chromatography; (column) 6:1 hexane/ethyl acetate, 4:1 hexane/ethyl acetate, 1:1 hexane/ethyl acetate. yield; 293mg, 20%. An analytical sample was recrystallized from toluene to give a yellow waxy solid.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.80 (3H, s); 4.60 (2H, d); 5.48–5.51 (1 H m), 6.53 (1H, s, D_2O exch.); 7.19 (1H, d, J = 8.5Hz); 7.64 (1H, d, J = 8.5Hz); 9.80 (1H, s).

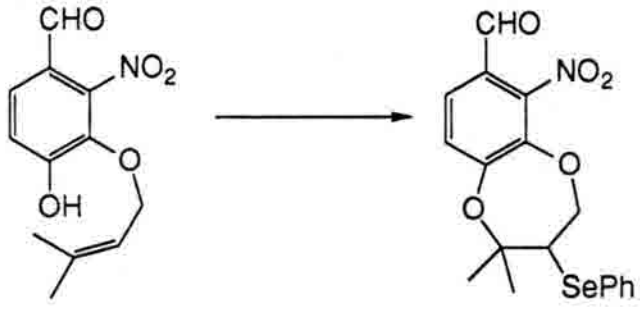
IR (KBr) 3090 (br), 1671, 1588, 1550, 1307, 1057, 890, 806 cm^{-1}.

microanalysis calc'd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58 Found: C. 57.49; H, 5.41; N, 5.67.

m.p. 99–100 °C.



181



181 **188**

(±)-3,4-Dihydro-2,2-dimethyl-6-nitro-3-(phenylseleno)-2*H*-1,5-benzodioxepin-7-carboxaldehyde (188)

A solution of N-PSP (123mg, 0.406mmol, 1.5eq) and camphorsulfonic acid (cat. amount) in CH_3CN (4.7mL) was added (dropwise) to a stirred solution of **181** (68.0mg, 0.270mmol, 1.0eq) in CH_3CN (1.8mL) at –23 °C, under N_2. After the addition was complete (10min), the reaction mixture was allowed to reach room temperature and stirred for 3 days. At this time the reaction mixture was recooled –23 °C and an additional amount of N-PSP (85.2mg, 0.282mmol, 1.04eq) in CH_3CN (3mL) was added to the reaction

flask. This mixture was allowed to reach room temperature and stirred one more day. It was then poured into a 1M NaOH solution and extracted with ether. The ethereal solution was washed with brine and dried over $MgSO_4$. After solvent removal, the crude yield was 117.9mg. chromatography; (radial) 1:10 ethyl acetate/hexanes yield; 57.4mg, 52%. An analytical sample was obtained by PTLC, 1:5 ethyl acetate/hexanes.

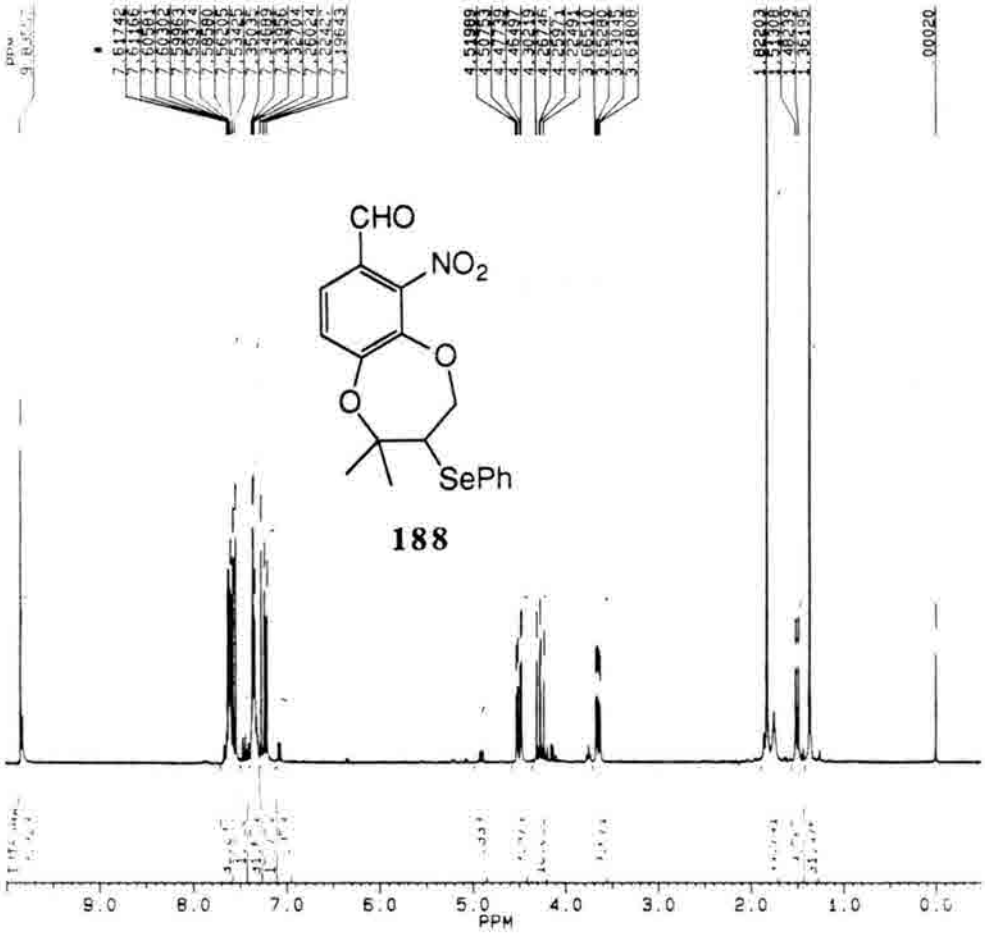
^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.36 (3H, s); 1.82 (3H, s); 3.64 (1H, dd, J = 3.7, 10.4Hz); 4.26 (1H, dd, J = 10.4, 12.8Hz); 4.49 (1H, dd, J = 3.7, 12.8Hz); 7.21 (1H, d, J = 8.4 Hz); 7.33–7.35 (3H, m); 7.55 1H, d, J = 8.4Hz); 7.58–7.62 (2H, m); 9.84 (1H, s).

IR (NaCl, neat) 2980, 1701, 1600, 1547, 1489, 1438,1371,1284 cm^{-1}.

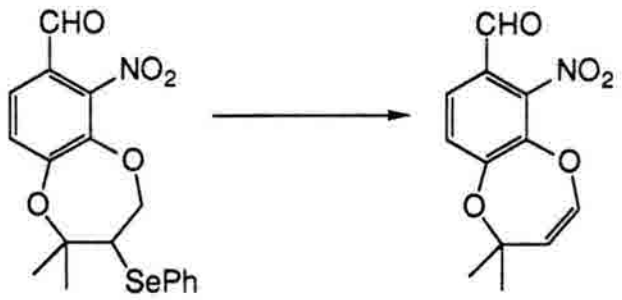
MS (EI) 406: m/e (relative intensity) 406 (0.5); 250 (8); 194 (8); 84 68); 49 (100).

microanalysis calc'd. for $C_{18}H_{17}NO_5Se$: C, 53.32; H, 4.22; N, 3.45 Found: C, 53.34; H, 4.35; N, 3.55.

m.p. oil.



188



188 **189**

2,2-Dimethyl-6-nitro-2*H*-1,5-benzodioxepin-7-carboxaldehyde (189)

To a stirred solution of **188** (32.5mg, 0.0800mmol, 1.0eq) in THF (1.0mL) at 0 °C was added m-CPBA (26.4mg, 0.153mmol, 1.9eq) After 21 hours the reaction mixture was poured into a separatory funnel, diluted with water and extracted with ether. The organic layer was washed three times with 10% $Na_2S_2O_3$, three times with sat. $NaHCO_3$ and once with brine. After drying, ($MgSO_4$) and solvent removal, the crude yield was 27.5mg. chromatography; PTLC, 1:20 ethyl acetate/hexane eluted three times, yield; 19.8mg, 99%.

To a stirred solution of the **188** (18.9mg, 0.046mmol, 1.0eq) in THF (0.5mL) was added H_2O_2 (0.064mL, 0.56mmol, 12eq, 30%) dropwise. After 2 hours the reaction mixture was poured into a separatory funnel, diluted with water and extracted with ether. The organic layer was washed with H_2O, brine and dried over $MgSO_4$ The solvent was removed leaving the pure product. yield; 7.9mg, 68%.

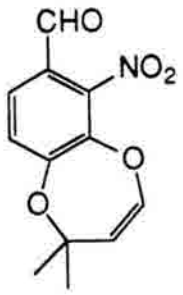
An analytical sample was recrystallized from cyclohexane to give yellow waxy crystals.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.50 (6H, s); 5.06 (1H, d, J = 7.5Hz); 6.34 (1H, d, J = 7.5Hz); 7.28 (1H, d, J = 8.5Hz); 7.59 (1H, d, J = 8.5Hz); 9.86 (1H, s).

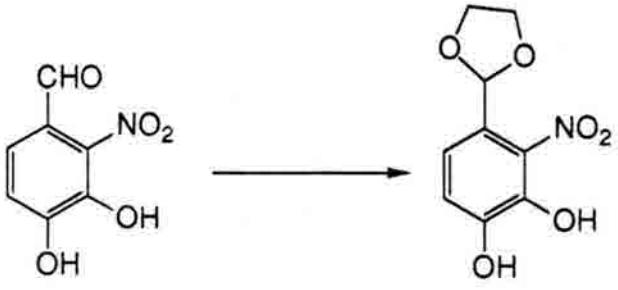
IR (neat) 2936, 2866, 1705, 1600, 1554, 1501, 1367, 1315, 1239, 1146, 1001 cm^{-1}.

microanalysis calc'd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62 Found: C, 57.96; H, 4.45; N, 5.51.

m.p. 96–98 °C.



189



186 **190**

4-(1,3-Dioxolan-2-yl)-3-nitro-1,2-benzenediol (190)

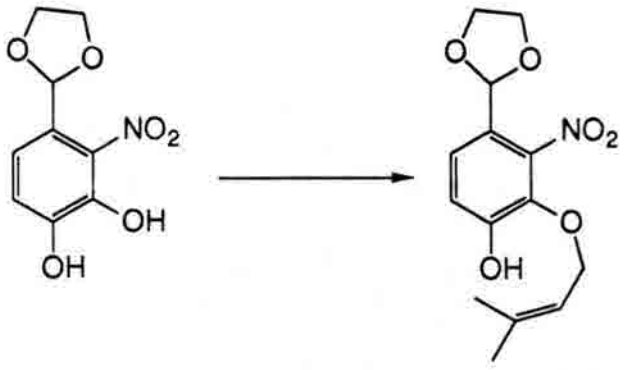
To a flask fitted with a dean stark trap and a reflux condenser was added **186** (1.50g, 8.22mmol 1.0eq) benzene (24mL) and ethylene glycol (0.5mL, 9.0 mmol, 1.1eq). The solution was refluxed 20h. The mixture was washed with H_2O and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness. yield; 1.90g, 100%. An analytical sample was recrystallized from THF/hexane to give a yellow crystalline solid.

^{1}H NMR (300 MHz) (DMSO-D_6) δTMS 3.50 (1H, br s, D_2O exch.); 3.88 (4H, s); 5.76 (1H, s); 6.87 (1H, d, J = 8.4 Hz); 6.93 (1H, d, J = 8.4 Hz); 10.15 (1H, s, D_2O exch.).

IR (KBr) 3280 (br), 2903, 1622, 1536, 1426 cm^{-1}.

microanalysis calc'd. for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.16. Found: C, 47.60; H, 3.93; N, 6.03.

m.p. 164–165 °C.



190 **191**

4-(1,3-Dioxolan-2-yl)-2-[(3-methyl-2-butenyl)oxy]-3-nitro-phenol (191)

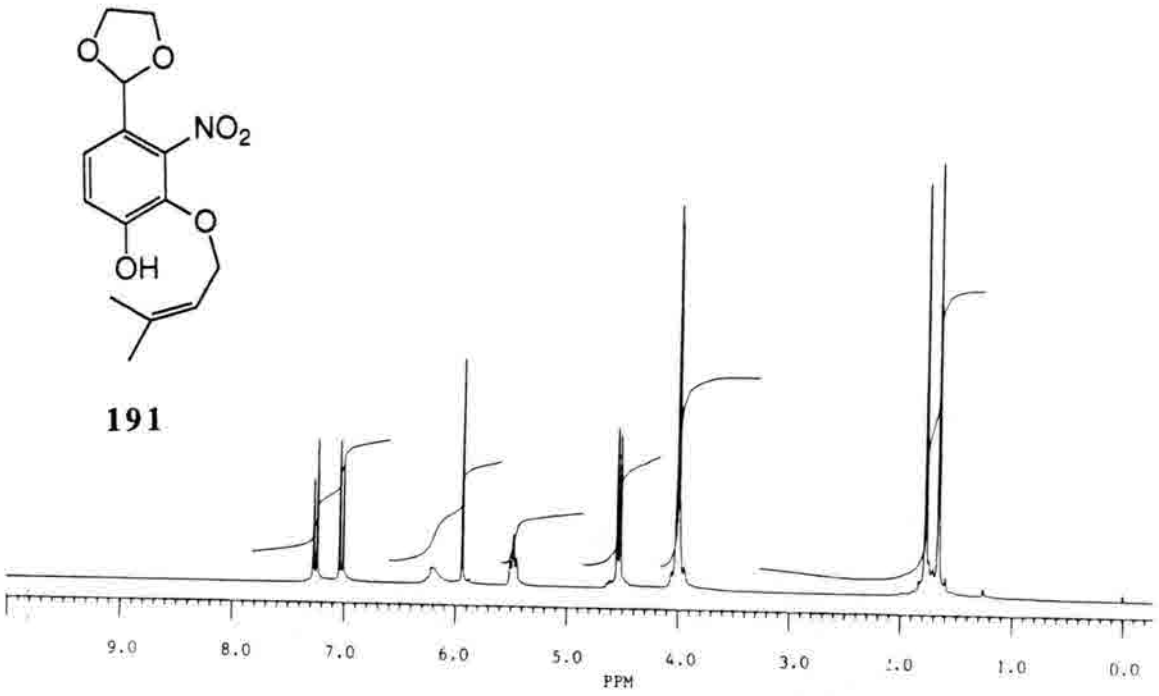
To a solution of **190** (786mg, 3.46mmol, 1.0eq) in DMF (8.6mL) was added K_2CO_3 (478mg, 3.46mmol, 1.0eq) at 0 °C under N_2. After 10 minutes prenyl bromide (0.45mL, 3.8mmol, 1.1eq) was added dropwise and stirred for 6.5 hours. The mixture was diluted with H_2O and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$, rotoevaporation gave a crude yield of 1.07g. chromatography; (flash column) 1:3 ethyl acetate/hexanes, yield; 730mg, 71%.

^{1}H NMR (300 MHz) ($CDCl_3$) δTMS 1.68 (3H, s); 1.79 (3H, s); 3.98–4.03 (4H, m); 4.54 (2H, d, J = 7.6 Hz); 5.48–5.54 (1H, m); 5.93 (1H, s, D_2O exch.); 5.95 (1H, s); 7.06 (1H, d, J = 8.6Hz); 7.28 (1H, d, J = 8.6Hz).

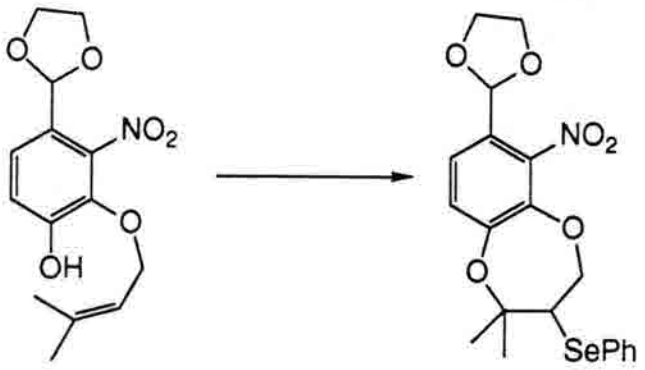
IR (NaCl, neat) 3388 (br), 2975, 2897, 1672, 1148 cm^{-1}.

EI HRMS m/e 295.1059 ($C_{14}H_{17}NO_6$ requires 295.1056).

m.p. oil.



191



191 **192**

(±)-7-(1,3-Dioxolan-2-yl)-3,4-dihydro-2,2-dimethyl-6-nitro-3-(phenylseleno)-2*H*-1,5-benzodioxepin (192)

A solution of N-PSP (284mg 0.941mmol, 1.5eq) in CH_3CN (17.7mL) was slowly (10 min.) added to a stirred solution of **191** (185.2mg, 0.627mmol, 1.0eq) in CH_3CN (4.45mL) at –23 °C, under N_2. The reaction was allowed to reach room temperature. After two days the reaction mixture was poured into a separatory funnel diluted with water

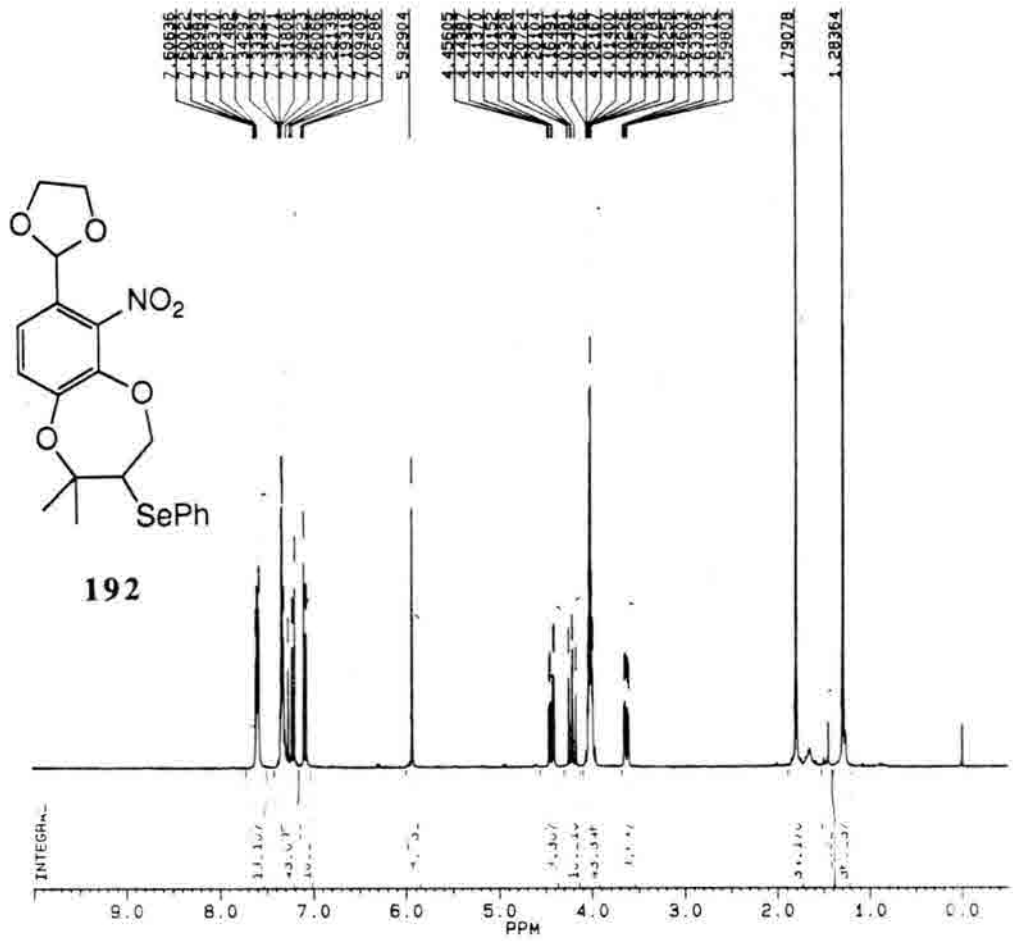
and extracted with ether. The organic layer was washed with 1M NaOH, brine, dried over $MgSO_4$. After evaporating the solvent, the crude yield was 273.5mg. chromatography (radial) 1:20 ethyl acetate/hexane (twice) yield; 132.0mg, 48%. An analytical sample was obtained by PTLC, 1:7 ethyl acetate/cyclohexane.

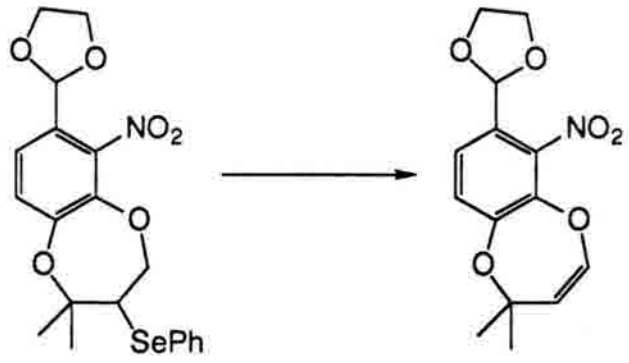
^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.28 (3H, s); 1.79 (3H, s); 3.62 (1H, dd, J = 3.6, 10.8Hz); 3.98–4.03 (4H, m); 4.20 (1H, dd, J = 10.8, 12.7Hz); 4.43 (1H, dd, J = 3.6, 12.7Hz); 5.93 (1H, s); 7.08 (1H, d, J = 8.5Hz); 7.21 (1H, d, J = 8.5Hz); 7.31–7.34 (3H, m); 7.57–7.61 (2H, m).

IR (NaCl, neat) 2978, 2895, 1536, 1494, 1374, 1285,1106,1023 cm^{-1}.

microanalysis calc'd. for $C_{20}H_{21}NO_6Se$: C, 53.33; H, 4.70; N, 3.11 Found: C, 53.44; H, 4.84; N, 3.12.

m.p. oil.





192 **193**

7-(1,3-Dioxolan-2-yl)-2,2-dimethyl-6-nitro-2*H*-1,5-benzodioxepin (193)

To a stirred solution of **192** (33mg, 0.073mmol, 1.0eq) in THF (1.0mL) at 0 °C was added $NaHCO_3$ (13.6mg, 0.162mmol, 2.0eq) followed by m-CPBA (27.9mg 0.162mmol, 2.0eq). The mixture was allowed to reach room temperature. After one day, the contents of the flask was poured into a separatory funnel diluted with ether and washed successively with 10% $Na_2S_2O_3$, sat. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated to give a crude yield of 27.5mg. chromatography; PTLC, 1:10 ethyl acetate/hexane eluted twice, yield; 19mg, 87%.

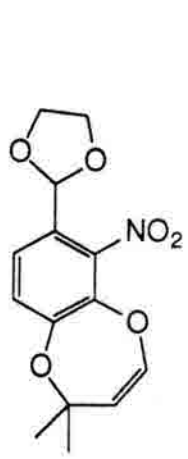
To a stirred solution of **192** (132.3mg, 0.294mg, 1.0eq) in THF (3.0mL) at 0 °C was added dropwise H_2O_2 (0.33mL 2.9mmol, 10.0eq, 30%). The solution was allowed to reach room temperature. After 18 hours the reaction mixture was poured into a separatory funnel, diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent removed to give a crude yield of 118.5mg. chromatography; 1:5 ethyl acetate/hexane, yield; 41.1mg, 48%. An analytical sample was obtained by PTLC, 1:10 ethyl acetate/cyclohexane.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.44 (6H, s); 4.00–4.03 (4H, m); 4.94 (1H, d, J = 7.6 Hz); 5.95 (1H, s); 6.29 (1H, d, J = 7.6Hz); 7.15 (1H, d, J = 8.5Hz); 7.25 (1H, d, J = 8.5Hz).

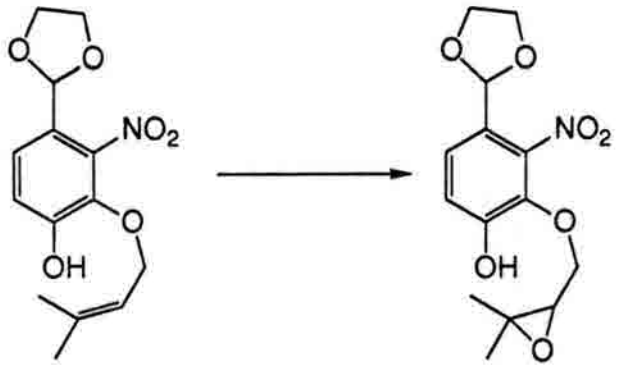
IR (NaCl, neat) 2999, 2895, 1703, 1664, 1540, 1500, 1370, 1311, 847, 748 cm^{-1}.

microanalysis calc'd. for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78; Found: C, 57.41; H, 5.21; N, 4.64.

m.p. oil.



193



191 **194**

(±)-2-[(3,3-Dimethyloxiranyl)methoxy-4-(1,3-dioxolan-2-yl)-3-nitrophenol (194)

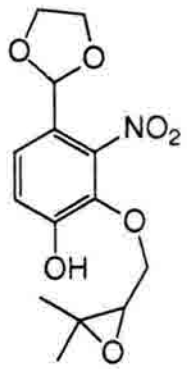
To a solution of **191** (354.2mg, 1.20mmol, 1.0eq) in CH_2Cl_2 (8mL) was added $NaHCO_3$ (153mg, 1.82mmol, 1.52eq) at 0 °C, under N_2. This was quickly followed by m- CPBA (319mg, 1.85mmol,1.54eq).The reaction mixture was allowed to reach room temperature and stirred for 11 hours. At this time the reaction was recooled to 0 °C with $NaHCO_3$ (100.7mg, 1.2mmol, 1.0eq), m-CPBA (206.9mg ,1.20mmol, 1.0eq) added, and stirred for four more hours . The mixture was poured into a separatory funnel, diluted with ethyl acetate, washed with a 1:1 solution of 10% $Na_2S_2O_3$, and sat. $NaHCO_3$, followed by two washings of 10% $Na_2S_2O_3$, 10% $NaHCO_3$, and brine. After drying over $MgSO_4$ and solvent removal the yield of epoxide was 405mg, 100%. An analytical sample was recrystallized from benzene to give a yellow crystalline solid.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.4 (3H, s); 1.44 (3H, s); 3.27 (1H, dd, J = 3.1, 8.2Hz); 3.83 (1H, dd, J = 8.2, 12.1Hz); 3.99–4.02 (4H, m); 4.63 (1H, dd, J = 3.1, 12.1Hz); 5.95 (1H, s); 7.07 (1H, d, J = 8.7Hz); 7.28 (1H, d, J = 8.7Hz).

IR (neat) 3278, 2969, 2897, 1588, 1452, 1372 cm^{-1}.

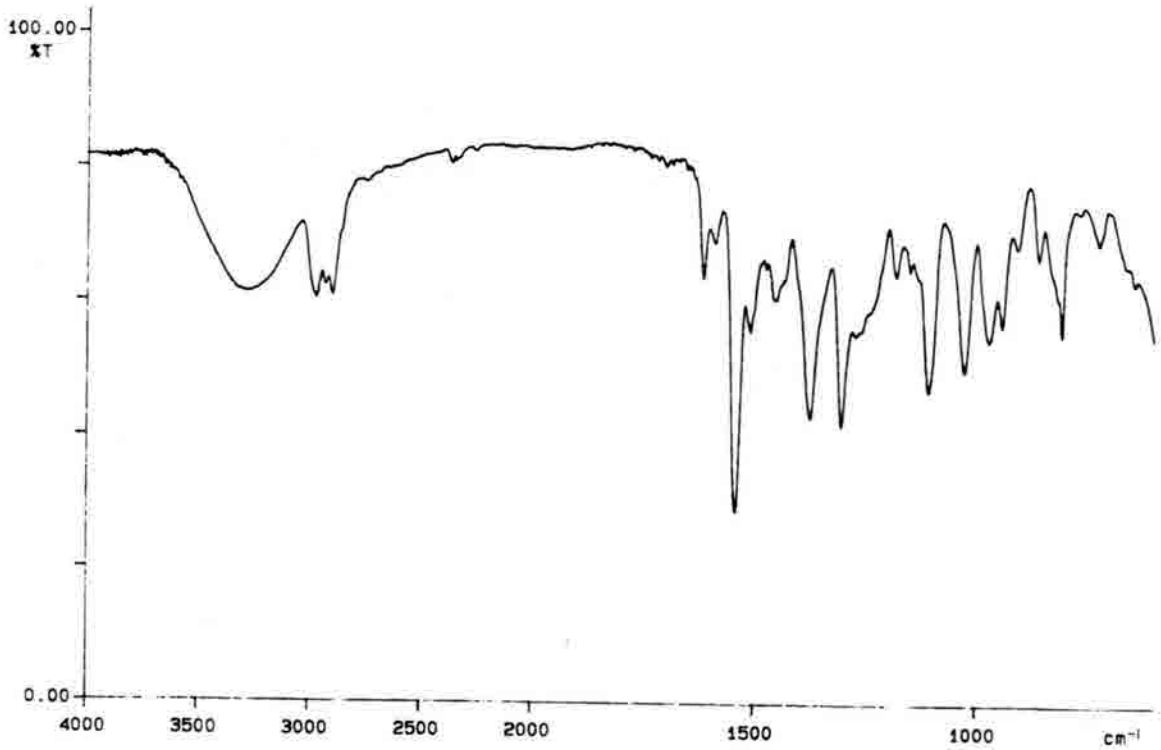
microanalysis calc'd. for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.08; H, 5.57; N, 4.47.

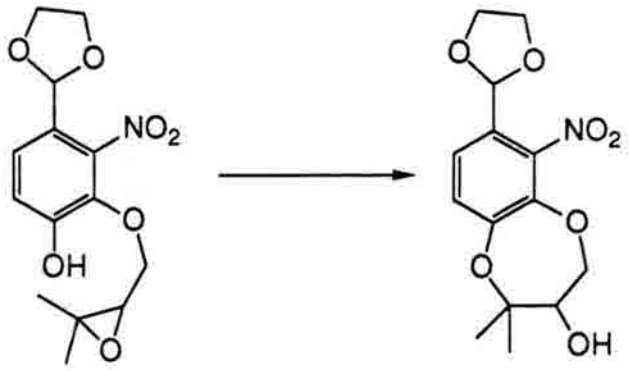
m.p. 125 °C.


O
O
NO2
O
OH
O

194

INTEGRAL
5.006
16.945
6.496
5.663
6.829
28.626
6.544
24.232
44.834
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


100.00
%T
0.00
4000
3500
3000
2500
2000
1500
1000
cm-1



194 **195**

(±)-7-(1,3-Dioxolan-2-yl)-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,5-benzodioxepin-3-ol (195)

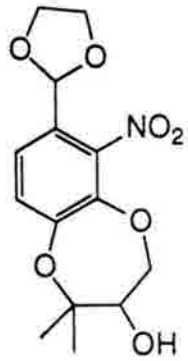
A flame dried flask flushed with Ar was charged with dry THF (13.5mL) to this was added $SnCl_4$ (0.135mL, 1.15mmol, 1.0eq). After 10 minutes **194** (357.9mg 1.15mmol, 1.0eq) in THF (1.5mL) was added dropwise. The solution was stirred for 1.5 hours, poured into a separatory funnel containing sat $NaHCO_3$, and extracted with ether. Solvent removal gave 368.5mg of a crude solid. chromatography; radial, 1:10 ethyl acetate/hexane yield; 109.7mg, 31%. An analytical sample was obtained by PTLC, 1:1 ethyl acetate/hexane.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.25 (3H, s); 1.54 (3H, s); 2.84 (1H, d, J = 11.1Hz , D_2O exch.); 3.63–3.68 (1H, m); 4.00–4.05 (4H, m); 4.18 (1H, dd, J = 1.4, 12.8Hz); 4.26 (1H, dd, J = 3.9, 12.8Hz); 7.12 (1H, d, J = 8.5 Hz); 7.26 (1H, d, J = 8.6 Hz).

IR (NaCl, neat) 1067, 3472, 2966, 2896, 1543, 1296 cm^{-1}.

microanalysis calc'd. for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.24; H, 5.68; N, 4.40.

m.p. 103–104 °C, (yellow waxy solid).



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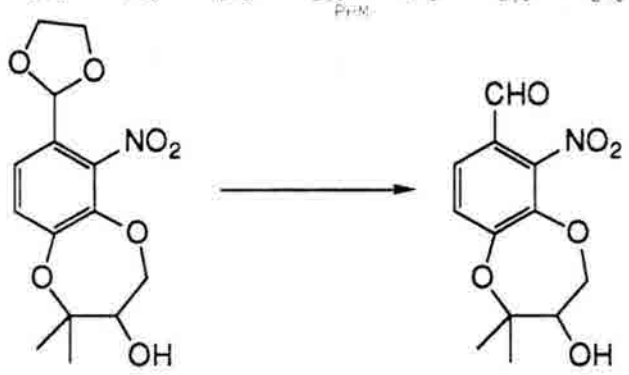


195 **196**

(±)-3,4-dihydro–3-hydroxy-2,2-dimethyl-6-nitro-2*H*-1,5-benzodioxepin-7-carboxaldehyde (196)

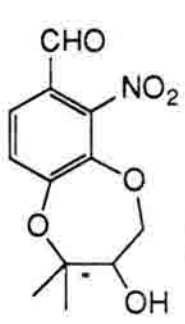
To a stirred solution of **195** (54.0mg, 0.173mmol, 1.0eq) in THF (0.72mL) was added HCl (0.35mL, 5%) at room temperature. After 27.5 hours the solution was diluted with ether washed with water (3x) brine (1x) and dried over $MgSO_4$ to give, after solvent removal 42mg of the crude product. chromatography; PTLC, 1:10 hexane/ethyl acetate, recrystallization; benzene, (yellow crystalline solid). yield; 34.4mg, 74%.

^{1}H NMR (300 MHz) ($CDCl_3$) δTMS 1.33 (3H, s); 1.58 (3H, s); 2.72 (1H, d, J = 10.6Hz , D_2O exch.); 3.75 (1H, ddd, J = 1.9, 3.8, 10.6Hz); 4.26 (1H, dd, J = 2.0, 12.8Hz); 4.32 (1H, dd, J = 3.9, 12.8Hz); 7.25 (1H, d, J = 6.6Hz); 7.60 (1H, d, J = 8.3Hz); 9.85 (1H, s).

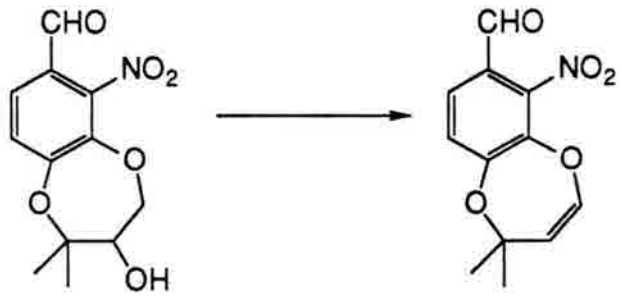
IR (KBr) 3575, 2991, 1702, 1603, 1542, 1489, 1444, 1300, 1277, 1246, 1140, 1034, 791 cm^{-1}.

microanalysis calc'd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.99; H, 5.00; N, 5.15.

m.p. 167–168 °C.



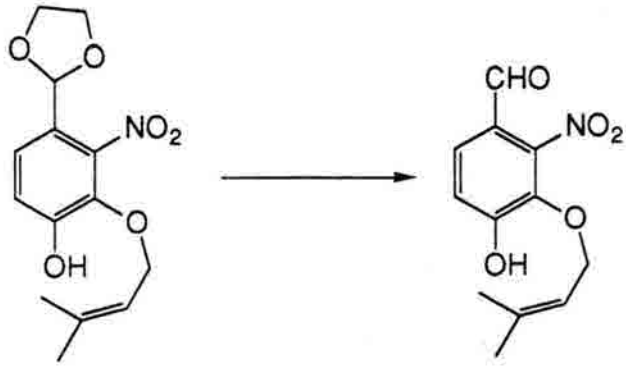
196



196 **193**

2,2-Dimethyl-6-nitro-2*H*-1,5-benzodioxepin-7-carboxaldehyde (193

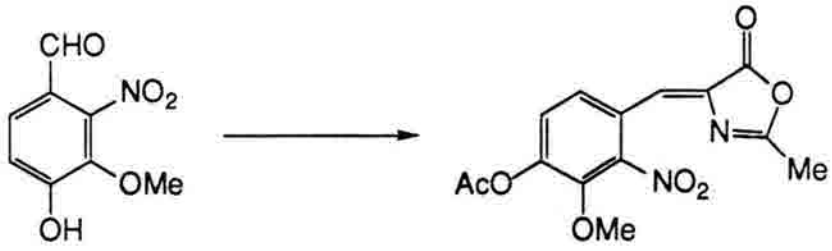
To a stirred solution of **196** (15.0mg, 0.056mmol, 1.0eq) in HMPA (0.3mL) at room temperature under N_2 was added at once MTPI (63.5mg, 0.14mmol, 2.5eq). The resulting solution was stirred vigorously for 3 days. The solution was then poured into a separatory funnel diluted with ethyl acetate, washed three times with H_2O, once with brine and dried over $MgSO_4$. After solvent removal the crude product was isolated. chromatography; PTLC, (1:5 ethyl acetate/hexane) yield; 6.0mg, 43%.



191 **181**

4-Hydroxy-2-[(3-methyl-2-butenyl)oxy]-3-nitro-benzaldehyde (181

To a stirred solution of **191** (52.6mg, 0.178mmol, 1.0eq) in THF (0.74mL) at room temperature, under N_2 was added HCl (0.36mL, 5%). After 1 day the solution was diluted with ether, washed with H_2O and brine. The solvent was removed, and the pure product was isolated. yield; 44.1mg, 99%.



131 **197**

1-[2-Methyl-(4H)-oxazolone-5-ylidene]methyl]-4-acetoxy-3-methoxy-2-nitrobenzene (197)

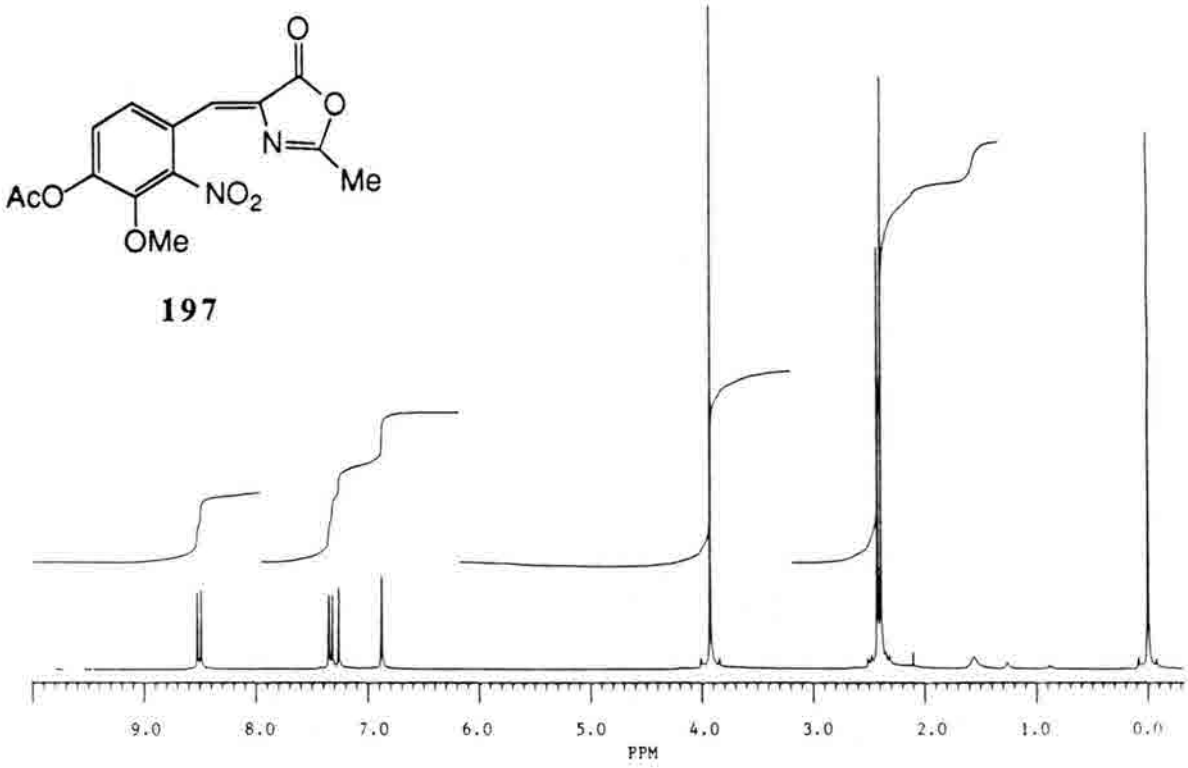
To a flask containing **131** (103g, 522mmol, 1.0eq), N-acetylglycine (104g, 887mmol, 1.7eq) and sodium acetate (103g, 1.25mol, 2.4eq) was added acetic anhydride (530mL). The mixture was vigorously shaken, then stirred for two days at 35 °C and at room temperature for two additional days. At this time the green-yellow material solidified. The flask was set aside for one day. It was then treated with H_2O (515mL) stirred 6 hours and placed in the refrigerator for a few days. The cold mixture was filtered and the crude yellow product washed with 6 liters of cold water the crude solid (110g) was recrystallized twice from acetic acid to give bright yellow rocky crystals. yield; 86g, 52%.

{when the same reaction was done with 16.9g of 2-nitrovanillin the yield was 58%}

^1H NMR (270MHz) ($CDCl_3$) δTMS 2.39 (3H, s); 2.42 (3H, s); 3.92 (3H, s); 6.88 (1H, s); 7.33 (1H, d, J = 8.8Hz); 8.50 (1H, d, J = 8.8Hz);

IR (KBr) 1758, 1720, 1664, 1532, 1409, 1371, 1288, 1116, 1048, 1020, 830 cm^{-1}.

(lit. ref. 68a, m.p. 215 °C, yellow crystals from acetic acid).



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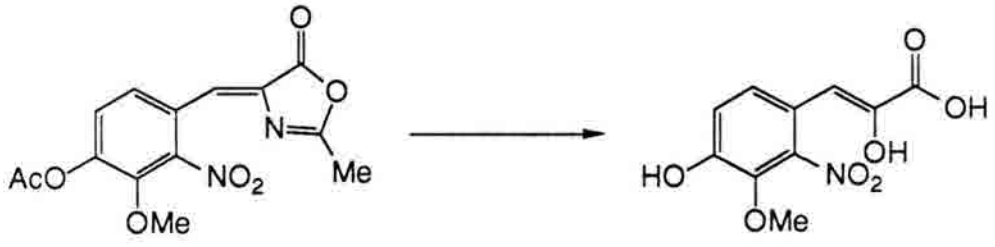


197 **198**

4-Hydroxy-3-methoxy-2-nitro-phenylpyruvic acid (198)

A solution of **197** (132g, 412mmol, 1.0eq) in H_2O (1.25L) HCl (310mL) and acetic acid (780mL) was refluxed vigorously in a 6L erlenmeyer flask (in the hood) for 1.5 hours. The volume of the flask was kept relatively constant (2.3L) by the addition of water. The flask was placed in the refrigerator and the product crystallized overnight. The fine yellow needles were collected and washed with cold water. yield; 87g, 83%. An analytical sample was recrystallized from acetic acid to give bright yellow needles. {When the same reaction was done with 21.2g of the phenylpyruvic acid, the yield was 88%}

^{1}H NMR (270MHz) (acetone-D_6) δTMS 3.92 (3H, s); 5.05–5.90 (2H, br s, D_2O exch.); 6.20 (1H, s); 7.16 (1H, d, J = 8.9Hz); 8.06 (1H, d, J= 8.8Hz); 8.50 (1H, s, D_2O exch.).

IR (KBr) 3420 (br), 1696, 1530, 1499, 1466, 1258, 973, 812 cm^{-1}.

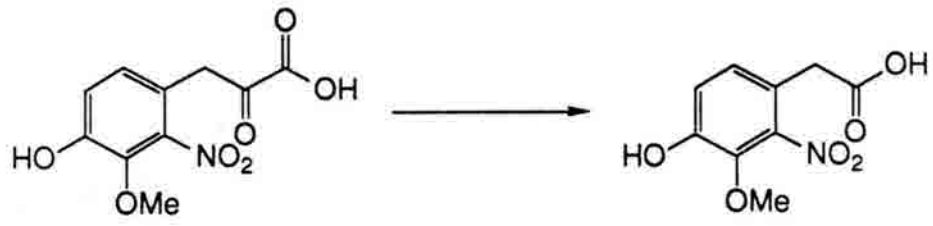
MS (EI) 255: m/e (relative intensity) 255 (1.3); 207 (0.4); 177 (13.8); 44 (100).

microanalysis calc'd. for $C_{10}H_9NO_7$: C, 47.07; H, 3.55; N, 5.49 found: C, 46.89; H, 3.71; N, 5.29.

m.p. 183–185 °C.

(lit. ref. 68a, m.p. 182 °C, yellow plates, acetic acid).

198



198 **199**

4-Hydroxy-3-methoxy-2-nitro-phenylacetic acid (199)

To a flask containing **198** (101g, 397mmol, 1.0eq) at 0 °C, was added a solution of NaOH (63.5g, 1.59mol, 4.0eq) in H_2O (1.37L). After 10 minutes hydrogen peroxide (49.5mL, 437mmol, 1.1eq, 30% solution/water) was added dropwise. The deep purple solution slowly turned brown during the addition. It was allowed to reach room temperature and stirred 24 hours. The reaction mixture was then acidified with concentrated HCl until the pH ≈3. A large amount of CO_2 was released and a fine yellow crystalline product precipitated. This was filtered, washed with cold H_2O and dried. yield; 72.6g, 81%. An analytical sample was recrystallized from H_2O to give bright yellow needles. {when the reaction was done with 11.9g of the phenylacetic acid the yield was 93%}

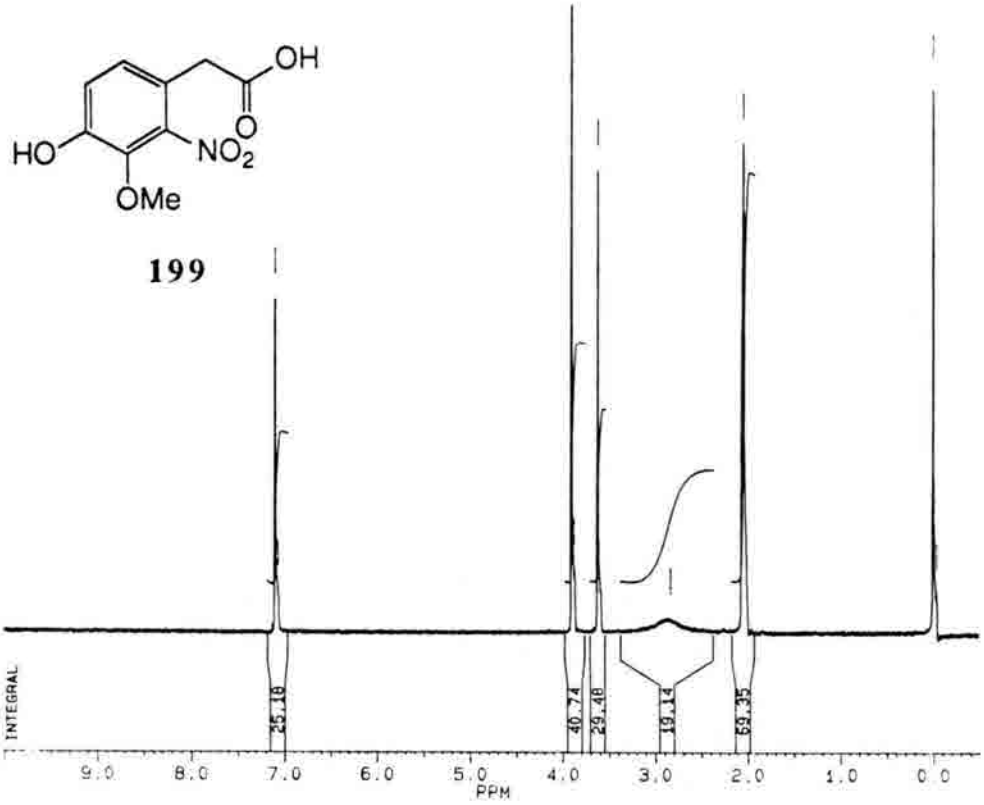
^1H NMR (300MHz) (acetone-D_6) δTMS 2.83 (2H, br s, D_2O exch.); 3.62 (2H,s); 3.91 (3H, s); 7.10 (2H, s)

IR (KBr) 3488,2958,2641,1668,1533,1399,1344,1296,1225,1051,825cm^{-1}.

MS (EI) 227 m/e (relative intensity) 228 (M^+, 0.7); 227 (5.8); 166 (10.0); 106 (13.6); 44 (100).

microanalysis calc'd. for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.16 found: C, 47.56; H, 4.06; N, 6.25.

m.p.161–162 °C.



199

199 **142**

1,3-Dihydro-6-hydroxy-7-methoxy-2*H*-indol-2-one (142)

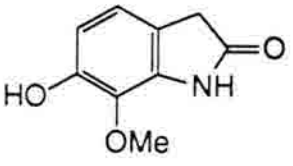
A mixture of **199** (23.0g, 101mmol, 1.0eq) glacial acetic acid (100mL) and Pd·C (10%, 1.5g) was hydrogenated at 40psi (the H_2 tank remained open during this time) in an oil bath (80 °C) for 5 hours. The mixture was immediately filtered through a celite plug and washed with a small amount of warm AcOH. The flask was kept under suction (cold) until a large quantity of white product had precipitated. This was filtered to collect the product, when an additional quantity of product precipitated under suction. This was collected and the two crops of white flakes combined and dried on the vacuum pump. yield; 17.2g, 95%. An analytical sample was recrystallized from H_2O to give white crystals.

^{1}H NMR (300MHZ) ($CDCl_3$) δTMS 3.50 (2H, d, J = 1.0Hz); 3.87 (3H, s); 5.49 (1H, s, D_2O exch.); 6.60 (1H, d, J = 8.1Hz); 6.86 (1H, d, J = 8.0Hz); 7.94 (1H, s, D_2O exch.)

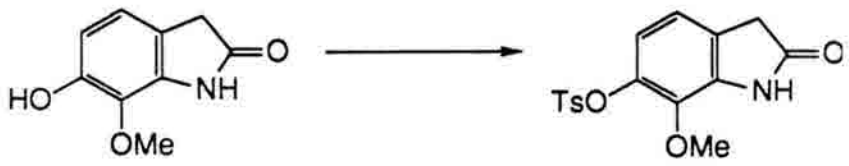
IR (Kbr) 3287, 3014, 2953, 1686, 1633, 1504, 1466, 1315, 1163, 637 cm^{-1}.

microanalysis calc'd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82 found: C, 60.51; H, 5.05; N, 7.60.

m.p. 210–211 °C.



142



142 **202**

1,3-Dihydro-7-methoxy-6-[(toluenesulfonyl)oxy]-2*H*-indol-2-one (202)

To a stirred mixture of **142** (321.6mg, 1.795mmol, 1.0eq) in acetone (7mL) at 0 °C under Ar, at –78 °C was added K_2CO_3 (740.5mg, 5.358mmol, 2.98eq) and toluenesulfonylchloride (376.4mg, 1.974mmol, 1.1eq) this was kept stirring for 5 hours at 0 °C and 1 hour at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed three times with 1M NaOH, once with brine, dried over $MgSO_4$, and concentrated to dryness. The product is a rusty solid. yield; 572.3mg, 96%.

^{1}H NMR (270MHz) ($CDCl_3$) δ 2.47 (3H, s); 3.52 (2H, s); 3.81 (3H, s); 6.70 (1H, d, J = 8.2Hz); 6.86 (1H, d, J = 8.1Hz); 7.34 (2H, d, J = 8.1Hz); 7.79 (2H, d, J = 8.3Hz); 7.85 (1H, s, D_2O exch.).

IR (KBr) 3172 (br), 1709, 1616, 1496, 1458, 1371, 1338, 1175, 1093, 1050, 1000, 848, 815, 728, 662, 548, cm^{-1}.

MS (EI) 333: m/e (relative intensity); 333 (5.0); 269 (1.4); 178 (40); 91 (77); 28 (100).

202 **204**

1,3-Dihydro-7-hydroxy-6-[(toluenesulfonyl)oxy]-2*H*-indol-2-one (204)

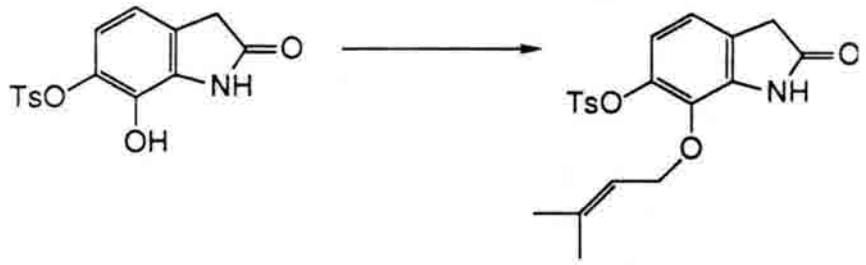
Boron tribromide (1.1mL, 1.1mmol, 2.0eq, 1M/CH_2Cl_2)was added to a stirred mixture of **202** (181.5mg, 0.5444mmol, 1.0eq) in methylene chloride (4.3mL) under Ar, at –78 °C. The mixture was stirred for 8 hours and placed in the freezer for 12 hours. The mixture was poured into ice/water, stirred for 0.5 hours and extracted with ethyl acetate.

The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness to give a red solid. yield; 164.7mg, 95%.

^1H NMR (270MHz) (acetone-D_6) δTMS 2.45 (3H, s); 3.43 (2H, d, J = 0.8Hz); 6.61 (1H, d, J = 8.1 Hz); 6.71 (1H, d, J = 8.1Hz); 7.46 (2H, d, J = 8.6Hz); 7.79 (2H, d, J = 8.3Hz); 8.50 (1H, s, D_2O exch.); 9.28 (1H, s, D_2O exch.).

IR (neat) 3259 (br), 2921, 1698, 1365, 1175, 1142, 728 cm^{-1}.

MS (EI) 319: (relative intensity); 319 (3.4); 278 (6.0); 246 (6.7); 163 (49); 139 (73); 91 (100).



204 **206**

1,3-Dihydro-7-[(3-methyl-2-butenyl)oxy]-6-[(toluenesulfonyl)oxy]-2*H*-indol-2-one (206)

To a stirred solution of **204** (159.4mg, 0.4992mmol, 1.0eq) in DMF (1.5mL) at 0 °C was added K_2CO_3 (103.5mg, 0.7488mmol, 1.5eq) followed by prenyl bromide (0.088mL, 0.75mmol, 1.5eq). After 4 hours the mixture was poured into water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated to dryness. chromatography; radial, 3:2 hexane/ethyl acetate, (reddish solid). yield; 71.9mg, 37%.

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.58 (3H, s); 1.70 (3H, s); 2.45 (3H, s); 3.52 (2H, s); 4.47 (2H, d, J = 7.3Hz); 5.35 (1H, t, J = 7.3Hz); 6.74 (1H, d, J = 8.2Hz); 6.87 (1H, d, J = 8.1Hz); 7.32 (2H, d, J = 8.0Hz); 7.79 (2H, d, J = 8.3Hz); 8.61 (1H, s, D_2O Exch.).

IR (neat) 3194 (br), 1714, 1627, 1464, 1376, 1196, 1175, 837, 728 cm^{-1}.

MS (EI) 387: m/e (relative intensity) 387 (16); 319 (16); 164 (37); 91 (91); 67 (100).

142 **203**

1,3-Dihydro-6-[(methanesulfonyl)oxy]-7-methoxy-2*H*-indol-2-one (203)

To a stirred solution of **142** (327.5mg, 1.828mmol, 1.0eq) in pyridine (3.6mL) at 0 °C was added methanesulfonylchloride (0.155mL, 2.010mmol, 1.1eq) dropwise. Five hours later the flask was placed in a refrigerator (7 °C) for two days. At which time HCl (28mL, 2M) was poured into the flask and the contents stirred an additional 0.5 hour. The mixture was then extracted with ethyl acetate washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give the product. yield; 410.1mg, 87%. An analytical sample was recrystallized from ethyl acetate, (orange crystals).

^1H NMR (270MHz) ($CDCl_3$) δTMS 3.21 (3H, s); 3.58 (2H, s); 3.95 (3H, s); 7.00 (2H, s); 8.47 (1H, s, D_2O exch.).

IR (KBr) 3183 (br) 1709, 1627, 1496, 1463, 1365, 1333, 1175, 1136, 1055, 1006, 973, 946, 837, 782, 750, 701, 652, 527 cm^{-1}.

MS (EI) 257: m/e (relative intensity) 257 (25); 178 (95); 163 (18); 106 (17); 28 (100).

microanalysis calc'd. for C, 46.69; H, 4.31; N, 5.44; found: C, 46.62; H, 4.42; N, 5.22.

m.p. 183–185 °C.

203 **205**

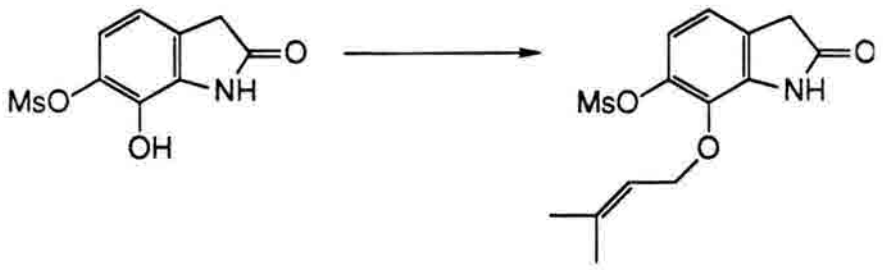
1,3-Dihydro-7-hydroxy-6-[(methanesulfonyl)oxy]-2*H*-indol-2-one (205)

To a stirred mixture of **203** (100.0mg, 0.3887mmol, 1.0eq) in methylene chloride (1.0mL) at –78° under Ar, was added boron tribromide (0.428mL, 0.428mmol, 1.1eq, 1M/CH_2Cl_2). After 2 hour and 40 minutes an additional amount of boron tribromide (0.428mL) was added. Six hours later the reaction mixture was poured into 20mL ice/water and stirred 0.5 hour more. The watery solution was extracted with ethyl acetate, washed with brine and dried over $MgSO_4$. The solvent was removed to give the spectrally pure product, (red solid). yield; 86.9mg, 92%.

1H NMR (270MHz) (acetone-D6) δTMS 3.34 (3H, s); 3.52 (2H, s); 6.85 (1H, s); 6.95 (1H, m); 8.69 (1H, s, D_2O exch.); 9.35 (1H, s, D_2O exch.).

IR (neat) 3215 (br) 1684, 1653, 1540, 1474, 1458, 1354, 1171, 1142, 1019, 962, 842 cm^{-1}.

MS (EI) 243: m/e (relative intensity) 243 (30); 163 (66); 136 (37); 64 (99); 28 (100).



205 **207**

1,3-Dihydro-6-[(methanesulfonyl)oxy]-7-[(3-methyl-2-butenyl)oxy]-2*H*-indol-2-one (207)

To a stirred solution of **205** (161.6mg, 0.6644mmol, 1.0eq) in DMF (2.0mL) at 0 °C under Ar was added K_2CO_3 (136.6mg, 0.9884mmol, 1.5eq) followed by prenyl bromide (0.10mL, 0.86mmol, 1.3eq). After 5 hours the solution was poured into water, extracted with ethyl acetate, washed with brine and dried over $MgSO_4$. The solvent was removed to give the spectrally pure product, (red solid). yield; 199.0mg, 96%.

^{1}H NMR (270MHz) ($CDCl_3$) δTMS 1.66 (3H, s); 1.76 (3H, s); 3.19 (3H, s); 3.59 (2H, s); 4.61 (2H, d, J = 7.4Hz); 5.58 (1H, quintet); 7.00 (2H, s); 9.38 (1H, D_2O exch.).

IR (KBr) 3194 (br), 1709, 1622, 1458, 1360, 1333, 1175, 842 cm^{-1}.

MS (EI) 311: (relative intensity) 311 (2); 243 (63); 164 (66); 69 (89); 28 (100).

142 **141**

1,3-Dihydro-6,7-dihydroxy-2*H*-indol-2-one (141)

Boron tribromide (800mL, 800mmol, 2.5eq, 1M /CH_2Cl_2) was added dropwise to a stirred mixture of **142** (57.3g, 320mmol, 1.0eq) in methylene chloride (640mL) under N_2 at –78 °C. The reaction mixture was stirred at –78 °C for 8 hours. It was then poured into a large (4L) beaker containing 1.5L of ice/water, stirred 10 minutes and filtered to remove undissolved product. The remaining liquid was extracted with ethyl acetate,

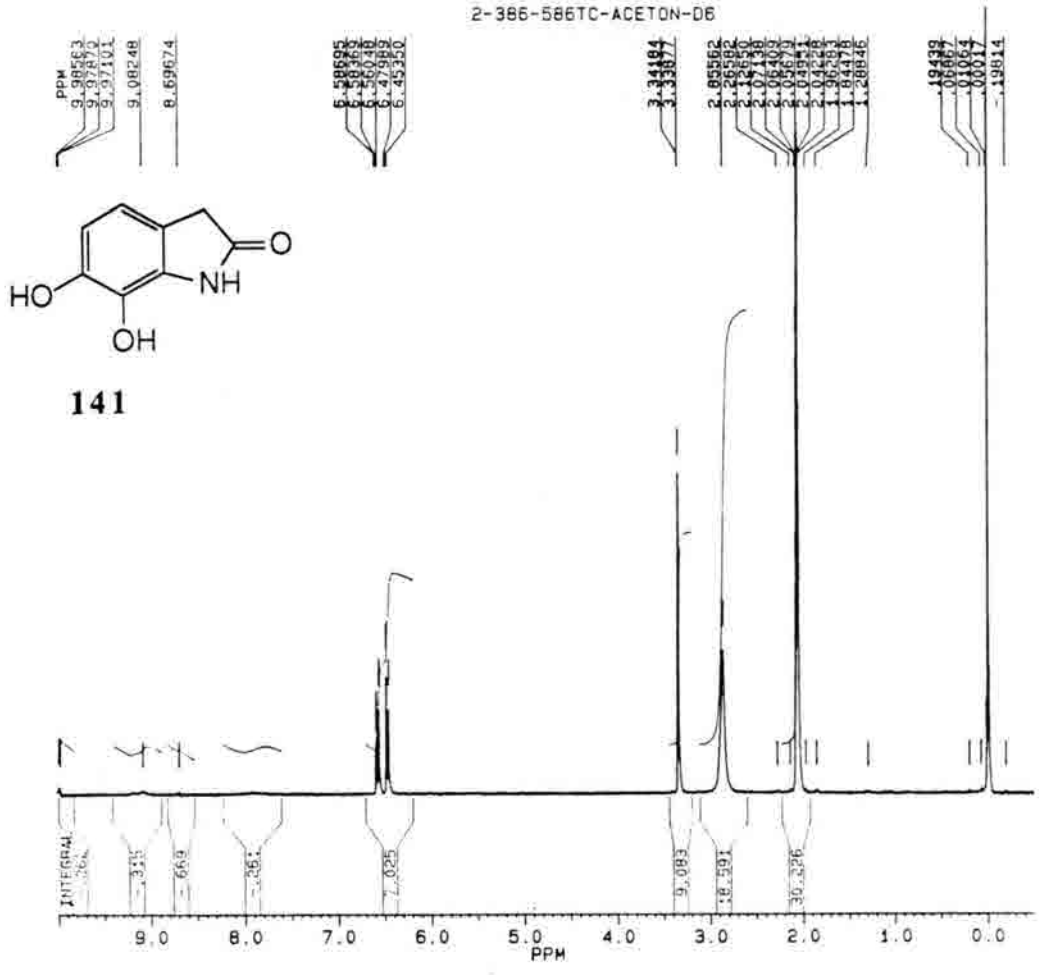
washed with brine and dried over $MgSO_4$. The organic layer was evaporated to yield the pure product which was combined with the filter cake. yield; 52.3g, 99%. An analytical sample was recrystallized from H_2O (three times) to give a pink crystalline solid.

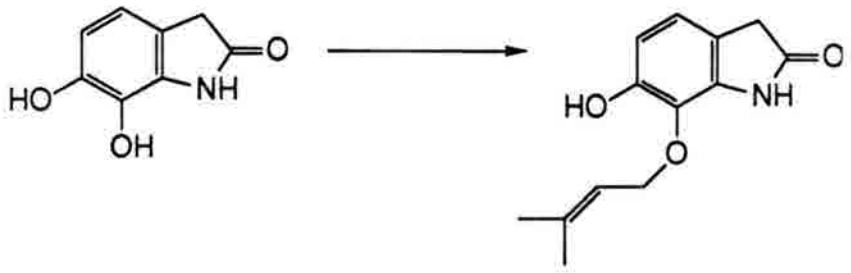
^1H NMR (300 MHz) (DMSO-D_6) δTMS 3.32 (1H, s); 6.36 (1H, d, J = 7.9Hz); 6.48 (1H, d, J = 2.9Hz); 8.80 (2H,br s D_2O exch.); 10.0 (1H, br s D_2O exch.)

IR (KBr) 3366–3123 (br), 1672, 1649, 1618, 1359, 1265, 1178, 786 cm^{-1}.

microanalysis calc'd. for $C_8H_7NO_3$: C, 58.18; N, 4.27; N, 8.48 found: C, 58.34; H, 4.44; N, 8.25.

m.p. decomposes 245 °C.





141 **208**

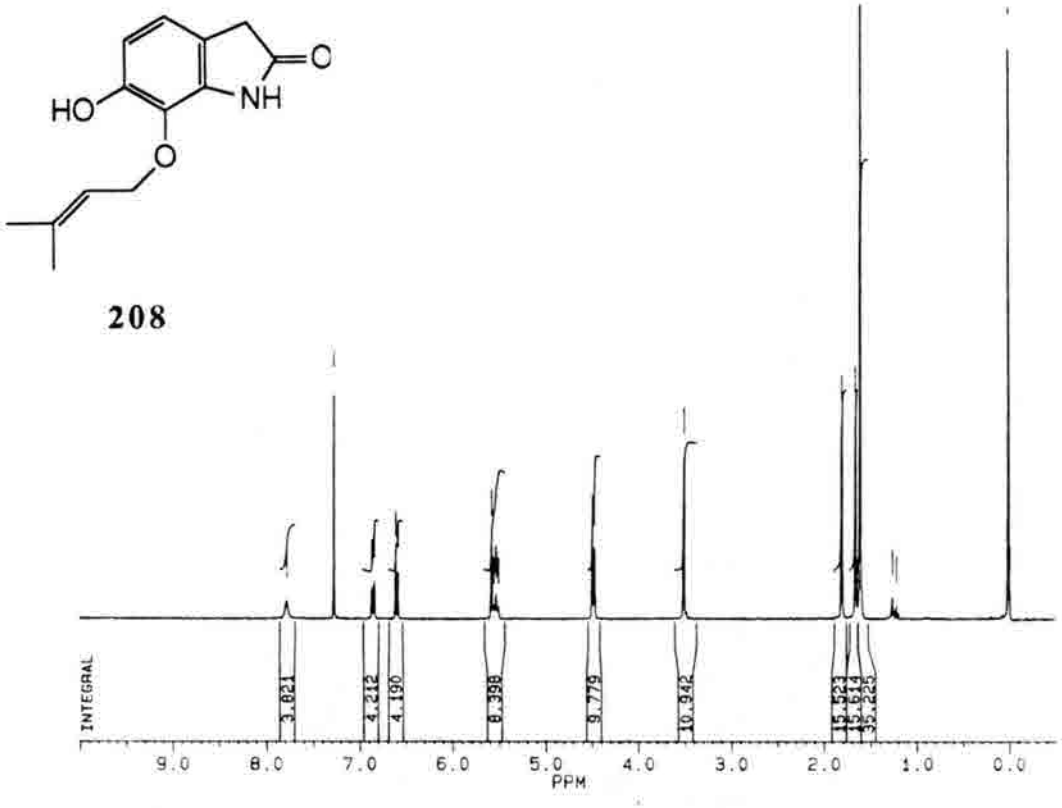
1,3-Dihydro-6-hydroxy-7-[(3-methyl-2-butenyl)oxy]-2*H*-indol-2-one (208)

To a stirred solution of **141** (36.9g, 223mmol, 1.0eq) in DMF (466mL) at 0 °C under N_2 was added K_2CO_3 (34.0g, 246mmol, 1.1eq). After 5 minutes prenyl bromide (28.4mL, 246mmol., 1.1 eq) was added dropwise. The reaction mixture was stirred overnight (0 °C to r.t.). It was then poured into a separatory funnel, diluted with H_2O and extracted with ether. The ethereal solution was washed with brine, dried over Na_2SO_4 and evaporated to dryness. chromatography; column 3:1 hexane /ethyl acetate, then 1:1 hexane/ethyl acetate, yield; 32.6g, 62%. To a stirred solution of 6,7-dihydroxyoxindole (19.0g, 115mmol, 1.0eq) in DMF (230mL) at 0 °C under Ar was added K_2CO_3 (15.9g, 115mmol, 1.0eq). After 8 minutes prenyl bromide (14.8mL, 127mmol., 1.1 eq) was added dropwise. The reaction mixture was stirred at 0 °C for 6.5h, it was then poured into a separatory funnel, diluted with H_2O and extracted with ether. The ethereal solution was washed with brine, dried over Na_2SO_4 and evaporated to dryness. chromatography; column 3:1 hexane /ethyl acetate, then 1:1 hexane/ethyl acetate, yield; 14.5g, 54%. An analytical sample was recrystallized from toluene to give a reddish–white solid.

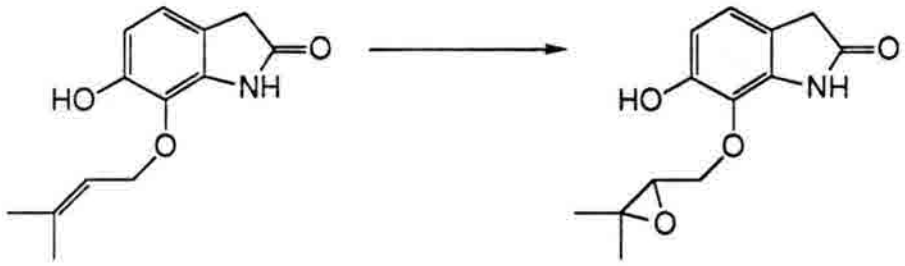
^{1}H NMR (300 MHz) ($CDCl_3$) δTMS 1.65 (3H, s); 1.80 (3H, s); 3.50 (2H, s); 4.47 (1H, d, J = 7.4Hz); 5.50–5.55 (1H, m); 5.57 (1H, s, D_2O exch.); 6.59 (1H, d, J = 8.1Hz); 6.84 (1H, d, J = 8.0Hz); 7.77 (1H, s, D_2O exch.).

IR (KBr) 3367, 3192, 2971, 1694, 1664, 1635, 1461, 1356, 1286, 1199, 1047 cm^{-1}.

microanalysis calc'd. for $C_{13}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33 Found: C, 65.16; H, 6.52; N, 6.07. m.p. 111 °C.



208



208 **212**

(±)-1,3-Dihydro-7-[(3,3-dimethyloxiranyl)methoxy]-6-hydroxy-2*H*-indol-2-one (212)

To a stirred solution of **208** (14.5g, 62.1mmol, 1.0eq) in CH_2Cl_2 (620mL) was added $NaHCO_3$ (5.7g, 68.3 mmol, 1.1eq) and m-CPBA (10.7g, 62.1mmol, 1.0eq). One hour later an additional amount of each reagent was added, $NaHCO_3$ (5.7g, 68.3 mmol, 1.1eq) and m-CPBA (10.7g, 62.1mmol, 1.0eq). This was stirred for one more hour and the reagents added again, $NaHCO_3$ (5.7g, 68.3 mmol, 1.1eq) and m-CPBA (10.7g, 62.1mmol, 1.0eq). This final mixture was stirred three more hours, while maintaining the temperature at 0 °C. It was then filtered into a flask containing 10% $Na_2S_2O_3$ and 10%

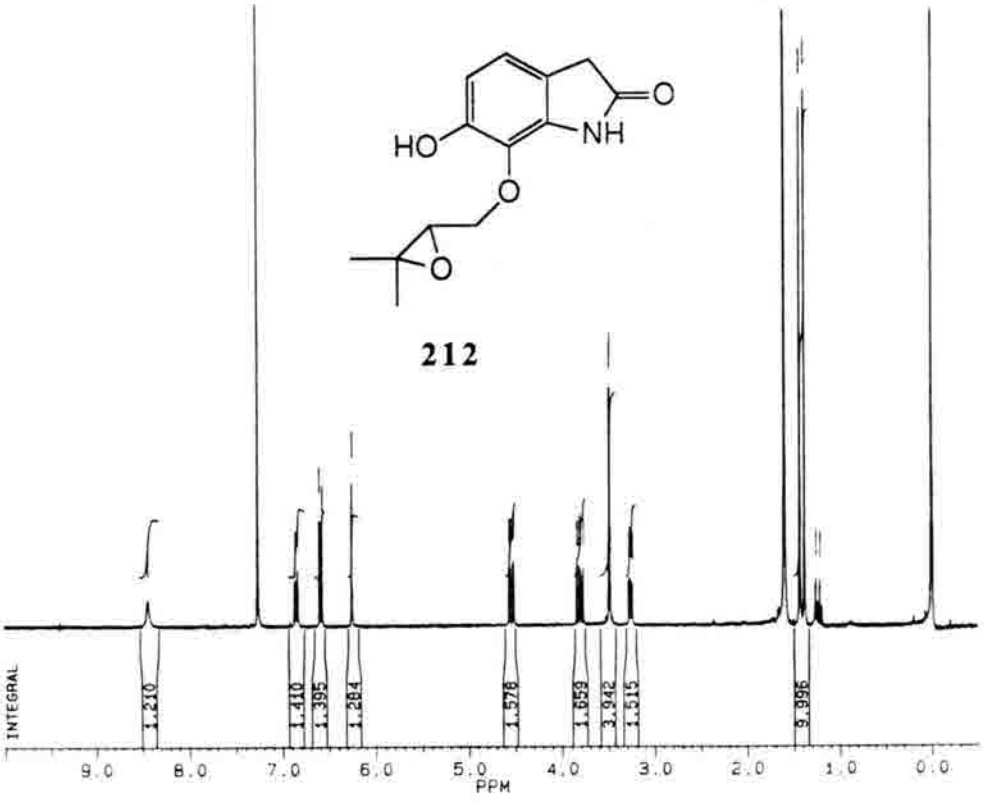
$NaHCO_3$. The organic layer was isolated, diluted with CH_2Cl_2, washed with 10% $Na_2S_2O_3$, sat $NaHCO_3$ and finally with brine. The organic layer was dried over Na_2SO_4, filtered, roto-evaporated and placed on the vacuum line. crude yield; 17g, used crude for the next step. An analytical sample was recrystallized from toluene to give a white solid.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.38 (3H, s); 1.42 (3H, s); 3.25 (1H, dd, J = 2.9, 8.5Hz); 3.47–3.49 (2H, m); 3.80 (1H, dd, J = 8.5, 12.0Hz); 4.54 (1H, dd, J = 2.9, 12.0Hz); 6.25 (1H, s, D_2O exch.), 6.58 (1H, d, J = 8.1Hz); 6.84 (1H, d, J = 8.1Hz); 8.44 (H, s, D_2O exch.).

IR (KBr) 3495, 3146, 2982, 1717, 1694, 1635, 1501, 1466, 1321, 1187, 1047, 861 cm^{-1}.

microanalysis calc'd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62 Found: C, 62.70; H, 6.15; N, 5.66.

m.p. 122–123 °C.



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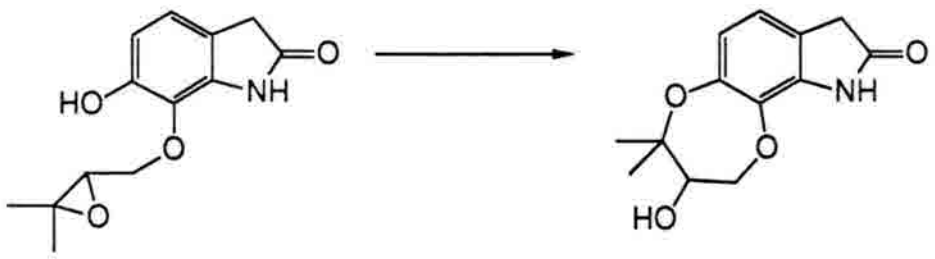


212 **124**

(±)-3,4,8,10,-Tetrahydro-3-hydroxy-4,4-dimethyl-2*H*,9*H*-[1,4]dioxepino[2,3-g]indol-9-one (124)

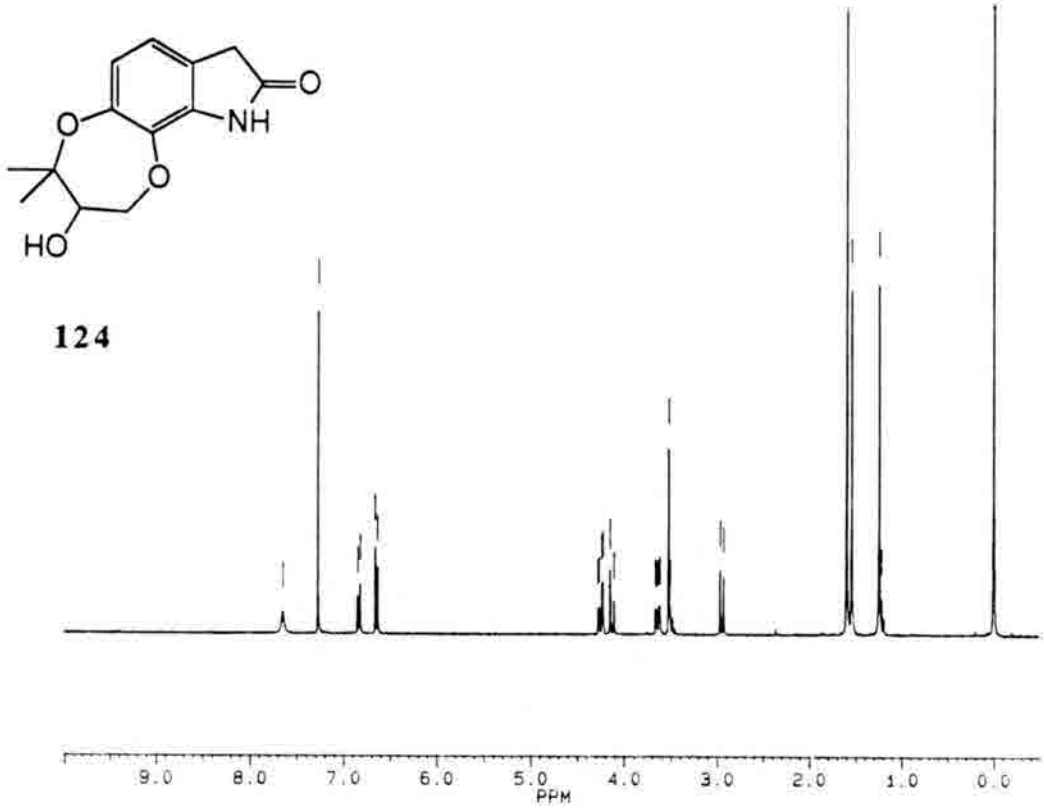
Tin tetrachloride (9.6mL, 81.8mmol, 1.2eq) was slowly added (dropwise) to a flame dried flask, flushed with Ar and charged with dry THF (960mL). After 10 minutes a solution of **212** (17g, 62.1mmol, 1.0eq) in THF (73mL) was added dropwise to the reaction vessel and stirred two hours. Approximately one half of the solvent was removed and the remaining solution poured into a separatory funnel containing (sat)$NaHCO_3$ and $H_2O \approx 50:50$ and exhaustively extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give a dark crude product. chromatography; column, 1:2 hexanes/ethyl acetate yield; 10g 64% for two steps. An analytical sample was recrystallized from toluene to give a yellow crystalline solid.

^1H NMR (300 MHz) ($CDCl_3$) δTMS 1.24 (3H, s); 1.54 (3H, s); 2.94 (1H, d, J = 11.2Hz, D_2O exch.); 3.51 (2H, s); 3.63 (1H, ddd, J = 1.0, 4.0, 11.2Hz); 4.12 (1H, dd, J = 1.0, 12.4Hz); 4.24 (1H, dd, J = 4.0, 12.5Hz); 6.64 (1H, d, J = 8.0Hz); 6.83 (1H, d, J = 7.9Hz ; 7.64 (1H, s, D_2O exch.).

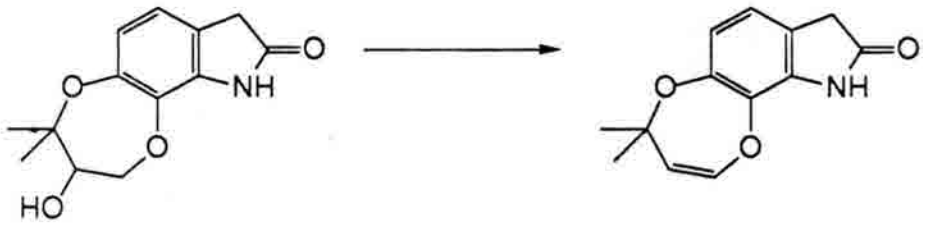
IR (KBr) 3460, 3320, 3169, 2982, 1711, 1682, 1461, 1327, 1216, 1047 cm^{-1}.

microanalysis calc'd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.08; N, 5.61 Found: C, 62.28; H, 6.21; N, 5.56.

m.p. 194 °C.



124



124 **217**

8,10-Dihydro-4,4-dimethyl-4*H*,9*H*-[1,4]dioxepino[2,3-g]indol-9-one (217)

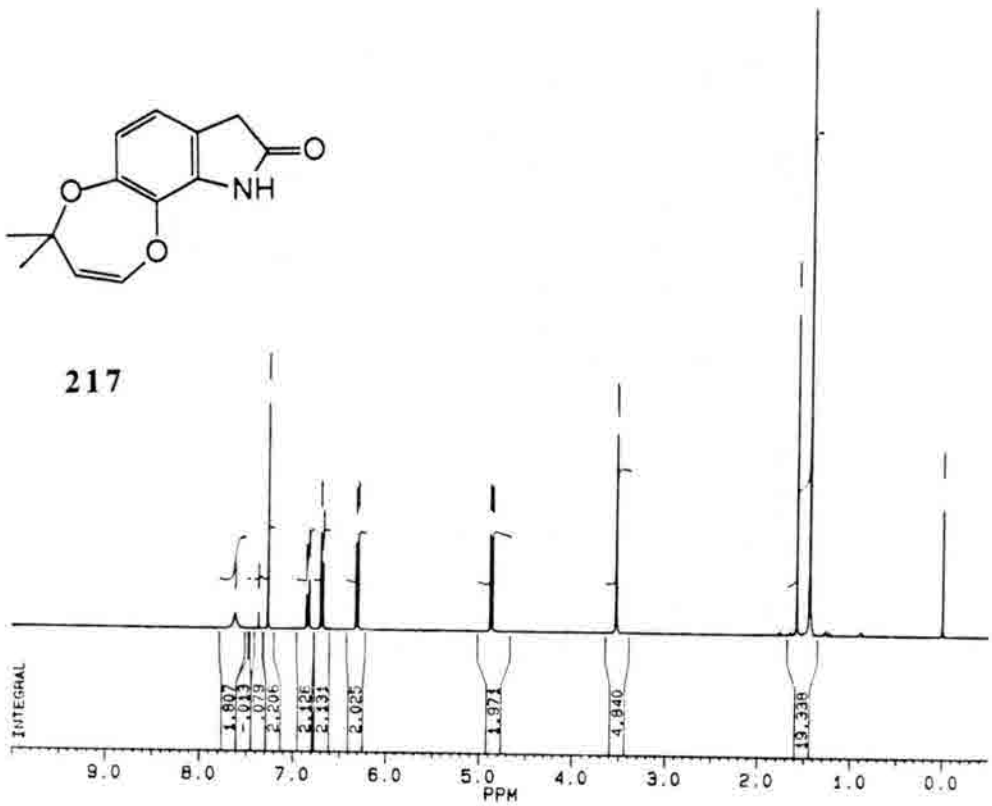
To a stirred solution of **124** (16.2mg, 0.065mmol, 1.0 eq) in HMPA (0.4mL) at room temperature under N_2 was added MTPI (69.6mg, 0.15 mmol, 2.4 eq). The dark red solution was stirred for 4 hours, poured into a separatory funnel, diluted with H_2O and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and reduced to dryness. chromatography; PTLC, 1:3 ethyl acetate/hexane eluted three times, yield; 8.8mg, 58%. An analytical sample was recrystallized from benzene to give a white solid.

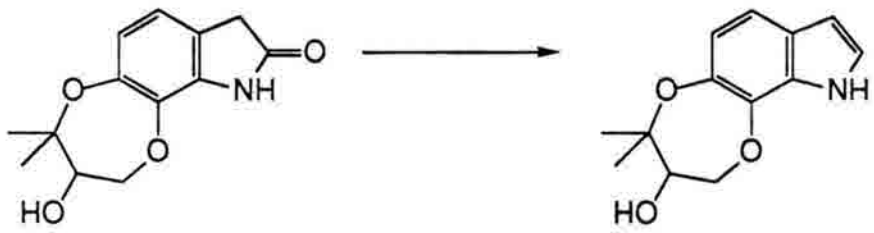
^{1}H NMR (300 MHz) ($CDCl_3$) δTMS 1.44 (6H, s); 3.53 (2H, s); 4.87 (1H, d, J = 7.7Hz); 6.31 (1H, d, J = 7.7Hz); 6.69 (1H, d, J = 8.0Hz); 6.84 (1H, d, J = 8.0Hz); 7.49 (1H, s, D_2O exch.).

IR (KBr) 3180, 2982, 1705, 1629, 1501, 1466, 1327, 1193, 1047, 750 cm^{-1}.

microanalysis calc'd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06 Found: C, 67.67; H, 5.80; N, 6.03.

m.p. 174–175 °C.





124 **125**

(±)-3-Hydroxy-4,4-dimethyl-3,4,10-trihydro-2*H*-[1,4]dioxepino[2,3-g]indole (125)

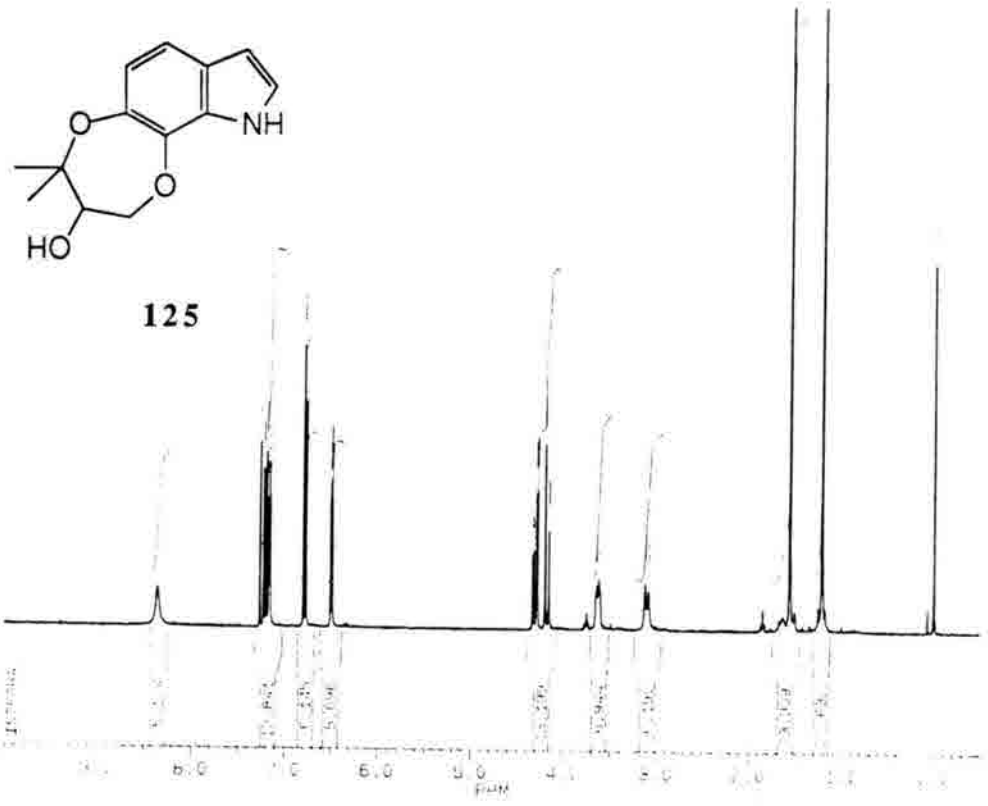
To a stirred solution of **124** (11.2g, 44.8mmol, 1.0eq) in THF (225mL) under Ar, at 0 °C was added $BF_3{\cdot}OEt_2$ (19.3mL, 157mmol, 3.5eq). After 10 minutes $NaBH_4$ (2.71g, 71.8mmol, 1.6eq) was added at once, stirred for 8 hours at 0 °C and then at room temperature for 40 additional hours. The reaction was completed by the slow addition of water (1.0L) and kept stirring for 0.5h. At this time HCl (conc.) was added until the pH = 1 and the mixture stirred an additional 0.5h. Then the mixture was basified (1M NaOH) until the pH = 14 and stirred a final 0.5h.The mixture was poured into a separatory funnel extracted with ethyl acetate/ether. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to leave 10g of a crude solid. chromatography; column, 2:1 hexane/ethyl acetate yield; 4.5g, 43%. An analytical sample was recrystallized from benzene and found to be a white crystalline solid.

^1H NMR (300MHz) ($CDCl_3$) δTMS 1.22 (3H, s); 1.56 (3H, s); 3.03 (1H, d, J = 11,4Hz, D_2O exch.); 3.63 (1H, ddd, J = 4.0, 0.9, 11.3Hz); 4.19 (1H, dd, J = 0.9, 12.3Hz); 4.31 (1H, dd, J = 4.0, 12.3Hz); 6.49 (1H, dd, J = 2.2, 3.1Hz); 6.78 (1H, d, J = 8.4Hz); 7.16–7.19 (2H, m); 8.29 (1H, s, D_2O exch.).

IR (KBr) 3340, 2984, 1580, 1504, 1444, 1338, 1224, 1133, 1057, 814, 753 cm^{-1}.

microanalysis calc'd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00 Found: C, 67.16; H, 6.63; N, 5.79.

m.p. 202–205 °C.



125

125 **219**

(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-3,4,10-trihydro-2*H*-[1,4]dioxepino[2,3-g]indole (219)

To a stirred solution of **125** (11.6g, 49.7mmol, 1.0eq) in DMF (124mL) at room temperature, under N_2 was added t-butyldimethylsilyl chloride (15.0g, 99.4mmol, 2.0eq) immediately followed by imidazole (23.7g, 348mmol, 7.0eq). The solution was slowly heated to 40 °C and stirred overnight. It was then poured into a separatory funnel and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed and the crude solid purified. chromatography;

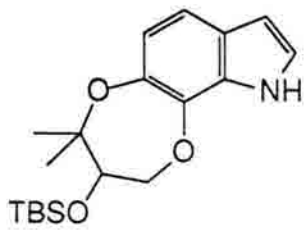
column, 5:1 hexane/ethyl acetate. yield; 14.2g, 82%. An analytical sample was recrystallized from cyclohexane to give a white solid.

^{1}H NMR (300Hz) ($CDCl_3$) δTMS 0.14 (6H, s); 0.89 (9H, s); 1.12 (3H, s); 1.48 (3H, s); 3.88 (1H, dd, J = 9.2, 11.5Hz); 3.98 (1H, dd, J = 3.2, 9.2Hz); 4,22 (1H, dd, J = 3.2, 11.5Hz); 6.48 (1H, dd, J = 2.2, 3.1Hz); 6.76 (1H, d, J = 8.4Hz); 7.14 (2H, ddd, J = 2.4, 3.4, 3.5Hz); 8.21 (1H, s, D_2O exch.).

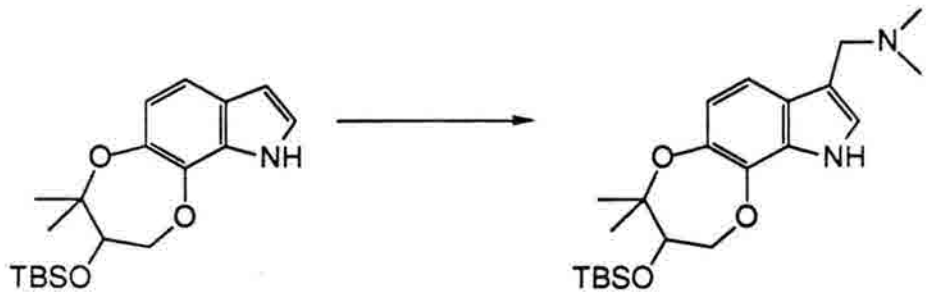
IR (neat) 3412,2936,1500,1438,1234,1093,833 cm^{-1}.

microanalysis calc'd. for $C_{19}H_{29}NO_3Si$: C, 65.66; H, 8.41; N, 4.03 Found: C, 65.59; H, 8.20; N, 3.90.

m.p. 118–119 °C.



219



219 **220**

(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-8-[(N,N-dimethylamino-yl)methyl]-3,4,10-trihydro-2*H*-[1,4]dioxepino[2,3-g]indole (220)

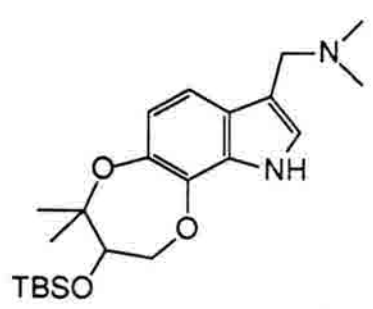
To a flask charged with acetic acid (136mL) under Ar, was added formaldehyde (3.4mL, 45mmol, 1.1eq, 37%/H_2O) and dimethyl amine (20.5mL, 163mmol, 4.0eq, 40% solution in H_2O) this was followed by **219** (14.2gmg, 40.9mmol, 1.0eq) after 10 minutes. The reaction mixture was stirred one day when 10% K_2CO_3 was added until the pH ≈ 8 then 2M NaOH was added. The mixture was extracted with ether/ethyl acetate, washed with brine and dried over Na_2SO_4. The solvent was removed leaving the pure product. yield; 17.3g, quant. An analytical sample was recrystallized from toluene to give a white flaky solid.

^{1}H NMR (300Hz) ($CDCl_3$) δTMS 0.90 (9H, s); 1.13 (3H, s); 1.48 (3H,s); 2.28 (6H, s); 3.58 (2H, s); 3.58 (2H, s); 3.88 (1H, dd, J = 9.2, 11.4Hz); 3.98 (1H, dd, J = 3.2, 9.1Hz); 4.21 (1H, dd, J = 3.2, 11.5Hz); 6.76 (1H, d, J = 8.4Hz); 8.44 (1H, s, D_2O exch.)

IR (neat) 2932, 1502, 1458, 1360, 1251, 1218, 1093, 837, 777 cm^{-1}.

microanalysis calc'd. for $C_{22}H_{36}N_2O_3Si$: C, 65.31; H, 8.97; N, 6.92 found: C, 65.09; H, 8.77; N, 6.73.

m.p. 152 °C.


N
NH
O
O
TBSO

220

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3.0
2.0
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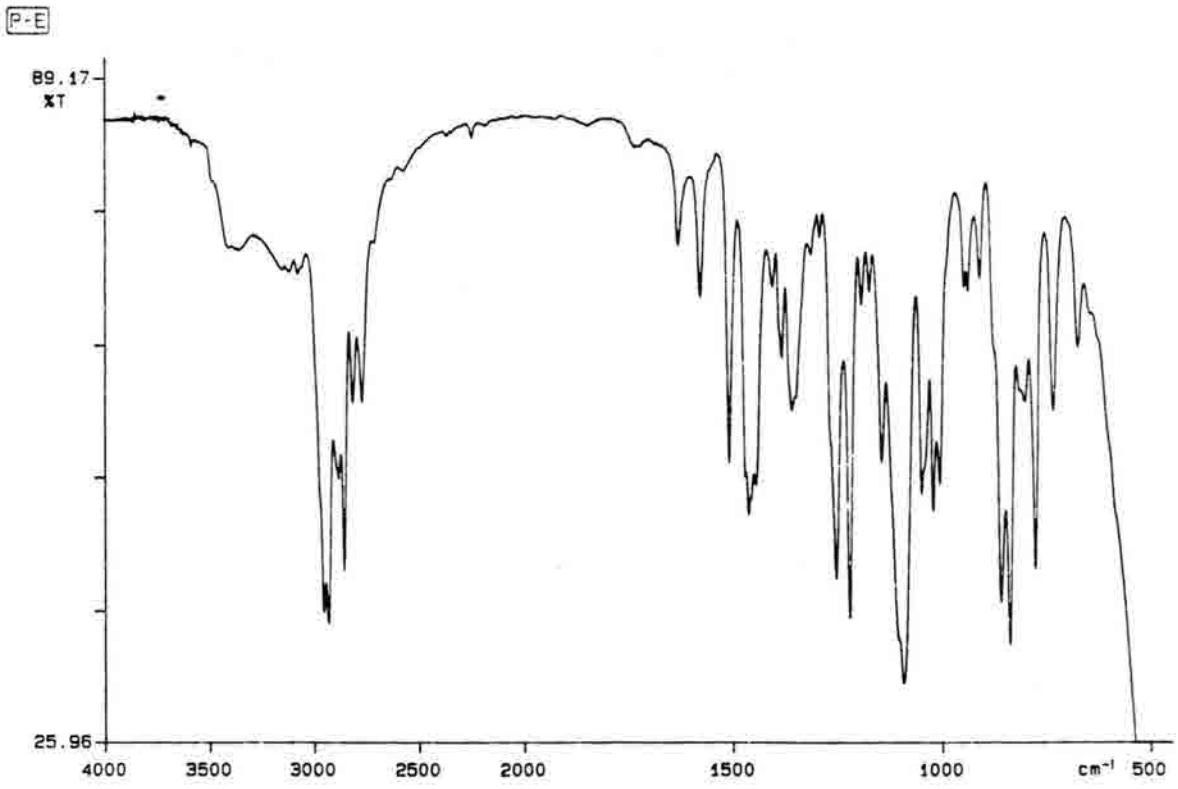
0.0
PPM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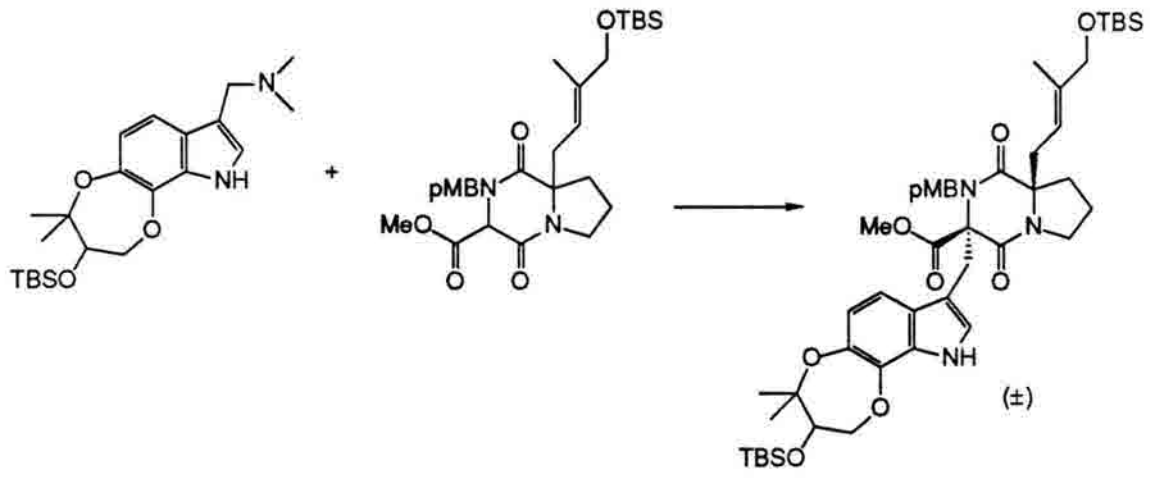
3500
3000
2500
2000
1500
1000
cm-1
500



220 **(221 & 222)** **223**

(±)-6(R)-[(2E)-Methyl-3-[[3-[[1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8a-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxo-pyrrolo[1,2-a]pyrazine-3-carboxylate (223)

To a stirred solution of **221&222** (23.0mg, 0.043mmol, 1.0eq) in CH_3CN (0.3mL) and PBu_3 (5.4μL, 0.022mmol,0.5eq) was added a solution of **220** (19.3mg, 0.048mmol, 1.1eq) in CH_3CN (0.3mL). This mixture was refluxed for 5.5 hours, and stirred at room temperature overnight. The reaction mixture was then diluted with ether, washed with water, dilute HCl, brine, and dried over $MgSO_4$. The solvent was removed and the crude oily solid purified. chromatography; (PTLC) 1:4 ethyl acetate/hexane, yield; 19.8mg, 51%. An analytical sample was recrystallized from cyclohexane to give a white crystalline solid.

^1H NMR (300MHz) ($CDCl_3$) δTMS 0.00 (6H, s); 0.01 (3H, s); 0.13 (3H, s); 0.14 (3H, s); 0.15 (3H, s); 0.034–0.19 (2H, m); 0.43–0.52 (2H, m); 0.62–0.72 (2H, m); 0.84 (9H, s); 0.85 (9H, s); 0.86 (9H, s); 0.88 (9H, s); 1.05 (3H,s); 1.45 (3H, s); 1.49 (3H, s); 1.537 (3H, s); 1.544 (3H, s);1.33–1.67 (2H, m); 2.14–2.25 (2H,m); 2.52–2.60 (2H,m); 2.87–3.03 (2H,m); 3.27 (6H, s); 3.36–3.52 (2H,m); 3.66 (1H, ½ ABq, J = 15.0Hz);

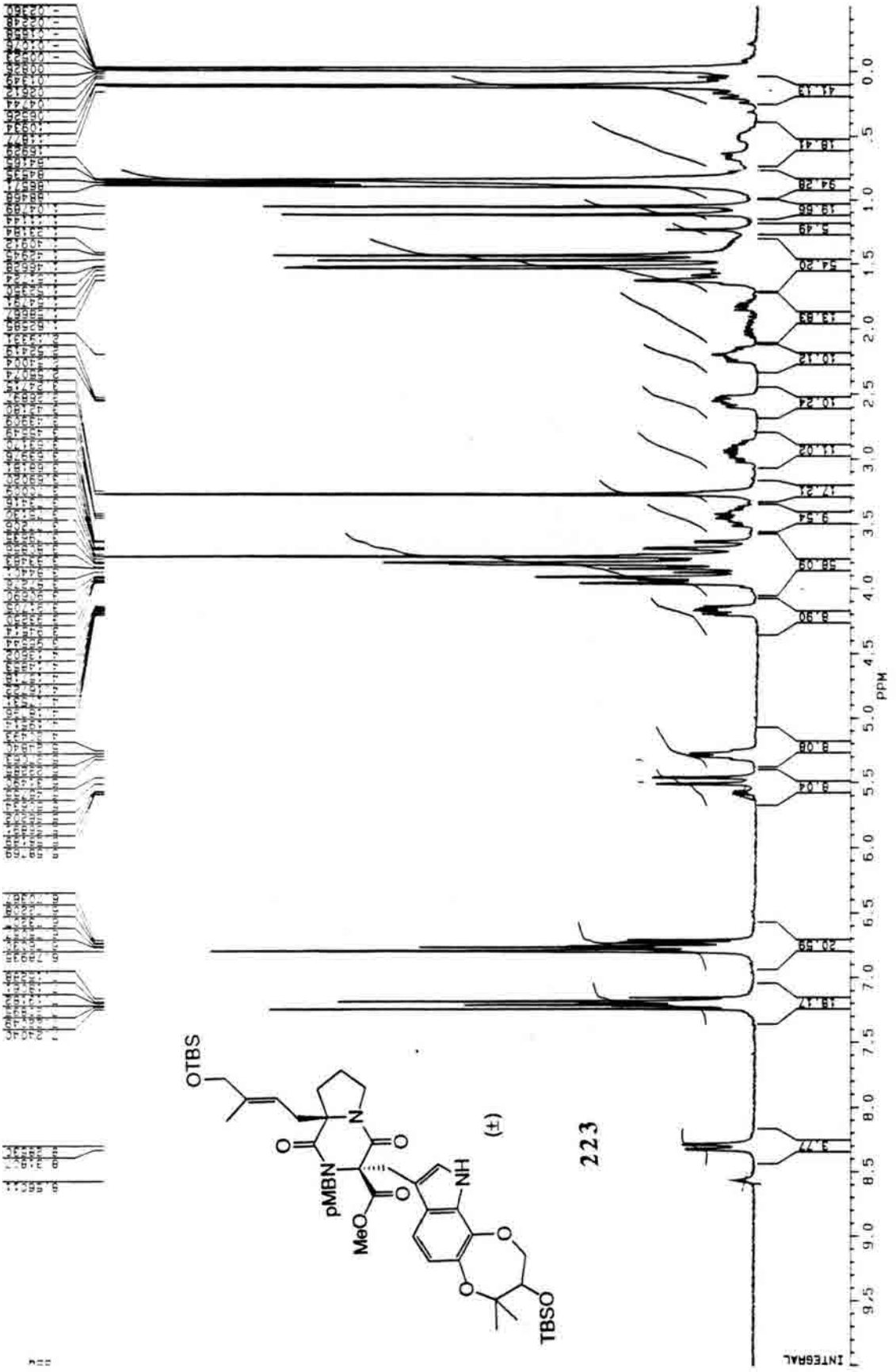
3.66 (1H, ½ ABq, J = 15.0Hz); 3.75 (6H, s); 3.77–3.96 (12H, m); 4.14–4.20 (2H,m); 5.25–5.31 (2H, m); 5.48 (2H, ½ ABq, J = 14.6Hz); 6.70–6.89 (8H,m); 7.15–7.22 (6H,m); 8.29 (1H, s, D_2O exch.); 8.32 (1H, s, D_2O exch.).

^1H NMR (300MHz) (D_6-acetone) δTMS 0.044 (6H, d, J = 3.0Hz); 0.066–0.20 (7H, m); 0.52–0.75 (1H, m); 0.88–0.93 (18H, m); 1.13 (3H,d, J = 6.7Hz); 1.45 (3H, m); 1.50–1.61 (4H, m); 2.24–2.32 (1H, m); 2.579 (1H, dd, J = 8.0,14.9Hz); 2.95–3.06 (1H, m); 3.26 (3H, d, J = 1.4Hz); 3.46–3.58 (1H, m); 3.67–3.87 (6H, m); 3.90 (2H, s); 3.97–4.01 (1H, m); 4.1 (1H, ½ABq, J = 15.2Hz); 4.15–4.24 (1H, m); 5.36 (1H, m); 5.51 (1H, ½ABq, J = 15.0Hz); 6.67 (1H, d, J = 8.3Hz); 6.86 (1H, d, J = 8.7Hz); 7.00 (1H, d, J = 2.2Hz); 7.15 (1H, dd, J = 2.6, 8.5Hz); 7.25 (1H, d, J = 8.6Hz); 10.19 (1H, s, D_2O exch.).

IR (neat) 3303, 2954, 2856, 1752, 1660, 1512, 1447, 1251, 1098, 1049, 837, 777 cm^{-1}.

microanalysis cacl'd. for $C_{48}H_{71}N_3O_9Si_2$: C, 64.76; H, 8.04; N, 4.72 Found: C, 64.95; H, 8.09; N, 4.53.

m.p. 168–168.5 °C.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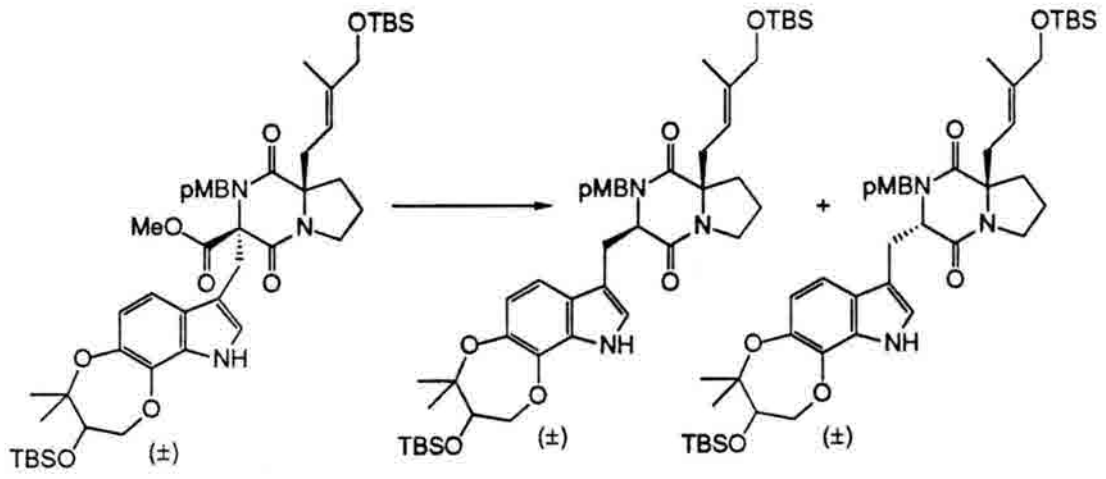
MeO
NH
TBSO
(±)
223
ppm



223 **225** **226**

[(±)-[3α,8aβ(E)]]8-[[2-[(4-Methoxyphenyl)methyl]-8a-[4-[[1,1-dimethylethyl)dimethylilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole (225)

[(±)-[3β,8aα(E)]]8-[[2-[(4-Methoxyphenyl)methyl]-8a-[4-[[1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole (226)

A clean dry flask containing **223** (24.4mg, 0.0274mmol, 1.0eq) and lithium chloride (11.6mg, 0.274mmol, 1.0eq) under N_2 was charged with HMPA (0.21mL) and water ($1.5x10^{-3}$mL, 0.0822mmol, 3.0eq). This mixture was heated to 100–105 °C for 2h. The resulting solution was diluted with 1:1 ethyl acetate/hexane, washed with water (5x) and brine. The organic layer was dried over $MgSO_4$, and concentrated to dryness. chromatography; (PTLC) 1:3 ethyl acetate/hexane, yield: **226** (an oily foam) 2.7mg, 12%; **225** (an oily foam) 8.9mg, 39% Total yield 51%.

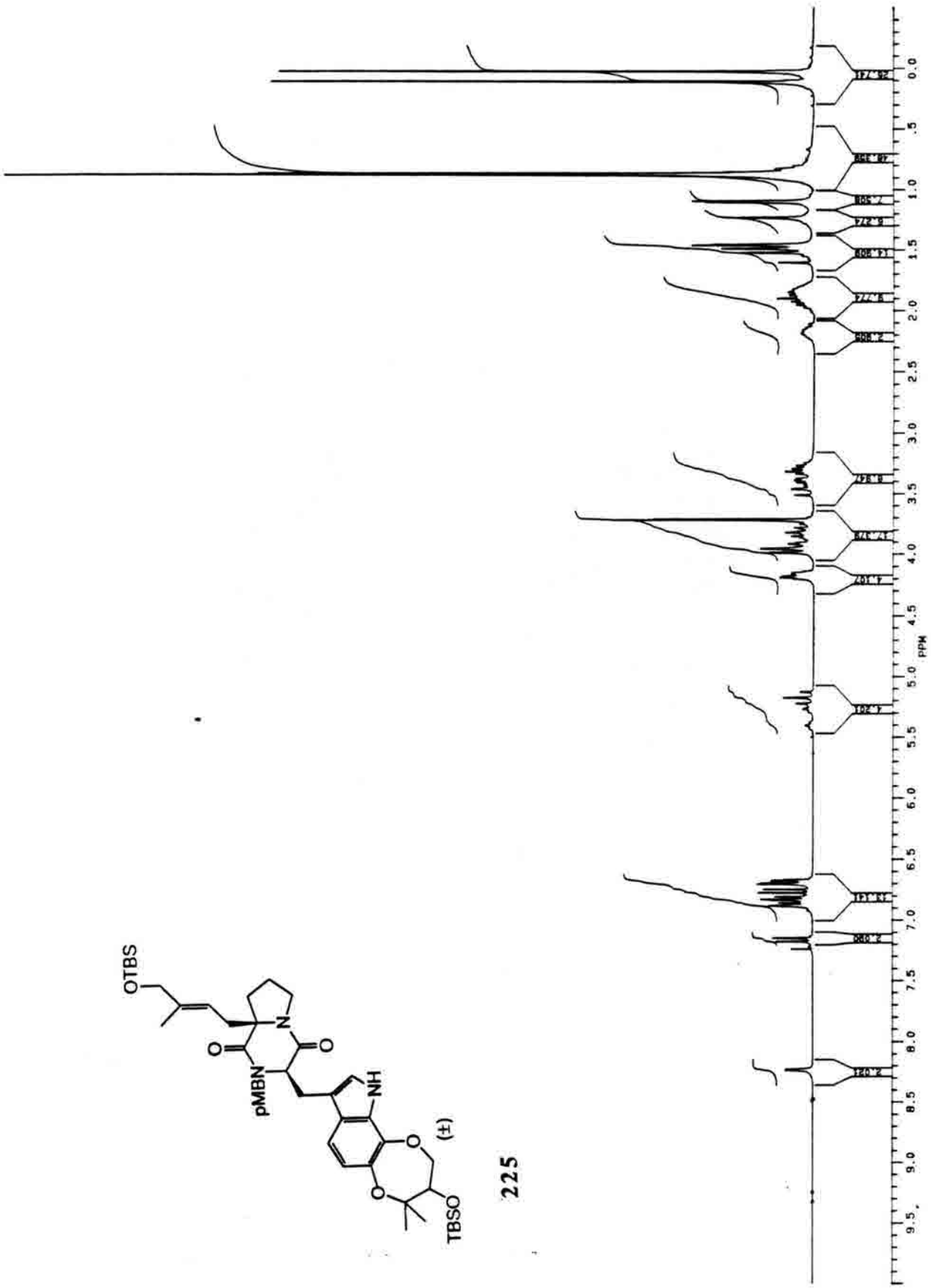
^{1}H NMR (300MHz) ($CDCl_3$) (**226**) δ –0.18 (12H, s); 0.12 (6H, s); 0.13 (6H, s); 0.26–0.41 (2H, m); 0.47–0.58 (2H, m); 0.62–0.72 (2H, m); 0.84 (18H, s); 0.87 (9H, s); 0.89 (9H, s); 1.06 (3H, s); 1.10 (3H, s); 1.44 (6H, s); 1.47 (3H, s); 1.48 (3H, s); 1.63–1.67 (2H, m); 2.10–2.17 (2H, m); 2.44–2.52 (2H, m); 2.89–3.05 (2H, m); 3.20–3.28 (2H, m); 3.40–3.5294H, m); 3.71–3.97 (16H, m); 4.08 (2H, br s); 4.14–4.21 (2H, m); 5.05 (2H, br s); 5.56 (1H, ½ ABq, J = 14.2Hz); 5.57 (1H, ½ ABq, J = 14.5Hz); 6.71 (1H, d, J = 8.6Hz); 6.73 (1H, d, J = 8.6Hz); 6.83–6.88 (6H, m); 7.14 (1H, d, J = 8.6Hz); 7.18 (1H, d, J = 8.6Hz); 7.22–7.23 (4H, m); 8.34 (2H, s, D_2O exch.)

IR *(anti)* (neat) 2932, 1649, 1508, 1455, 1250, 1220, 1103, 838 cm^{-1}.

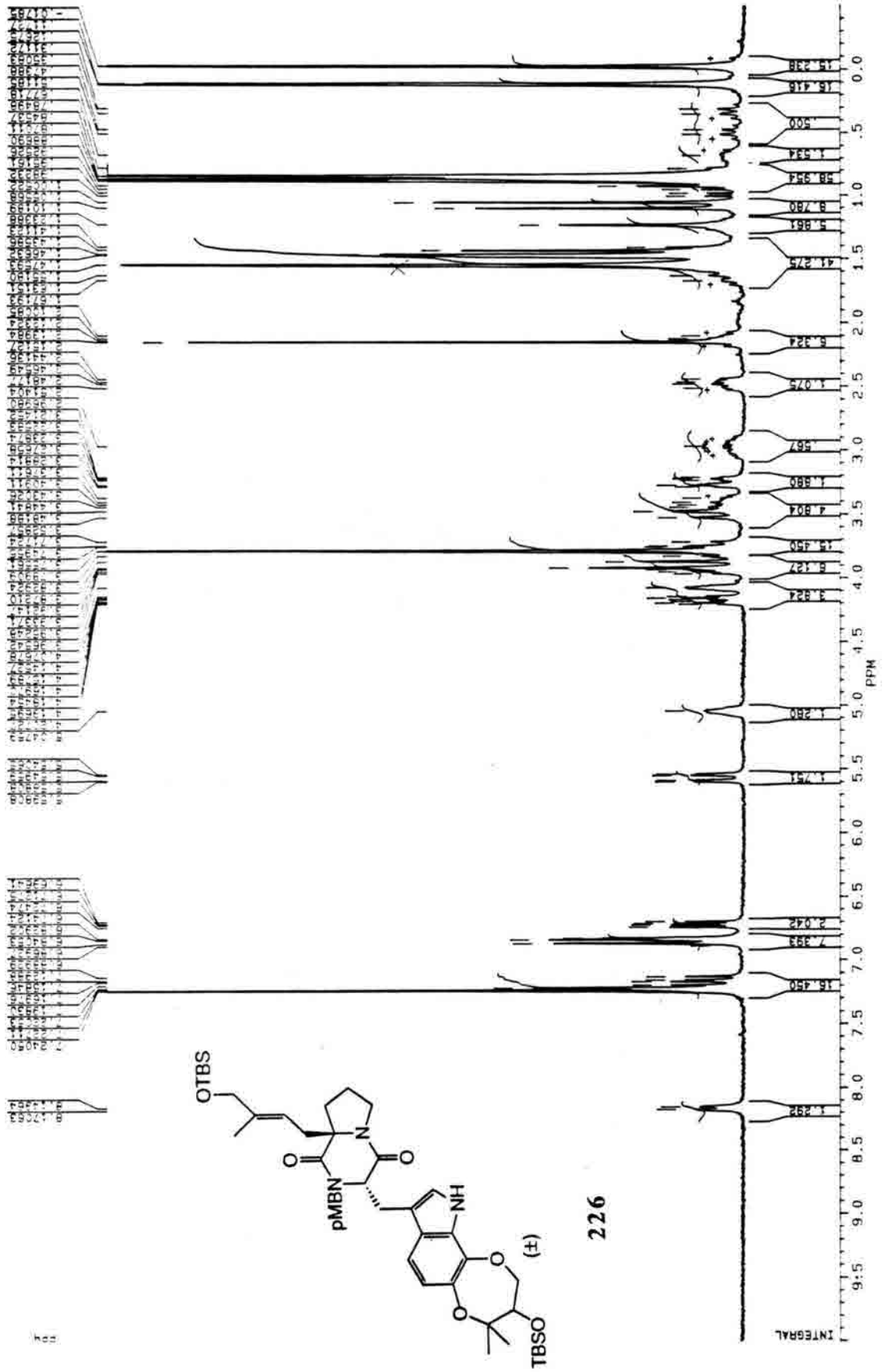
EI HRMS *(anti)* 831.46765 ($C_{46}H_{69}N_3O_7Si_2$ requires 831.4674)

^{1}H NMR (300MHz) ($CDCl_3$) (**225**) δ 0.036 (12H, s); 0.12 (6H, s); 0.13 (6H, s); 0.84 (9H, s); 0.87 (9H, s); 0.88 (9H, s); 0.882 (9H, s); 1.10 (3H, s); 1.11 (3H, s); 1.458 (3H, s); 1.463 (3H, s); 1.72–2.04 (10H, m); 2.12–2.23 (2H, m); 3.24–3.51 (8H, m); 3.72 (3H, s); 3.73 (3H, s); 3.79–3.82 (6H, m); 3.83 (2H, s); 3.86 (2H, s); 4.15–4.20 (4H, m); 5.15 (1H, ½ ABq, J = 14.2Hz); 5.20 (1H, ½ ABq, J = 14.2Hz); 5.28 (1H, m); 5.45 (1H, m); 6.67–6.71 (4H, m); 6.76 (2H, d, J = 8.5Hz); 6.81–6.90 (6H, m); 7.16 (2H, d, J = 8.5Hz); 8.12 (2H, s, D_2O exch.).

IR *(syn)* (neat) 2920, 1655, 1508, 1449, 1250, 1220, 1091, 838 cm^{-1}.



225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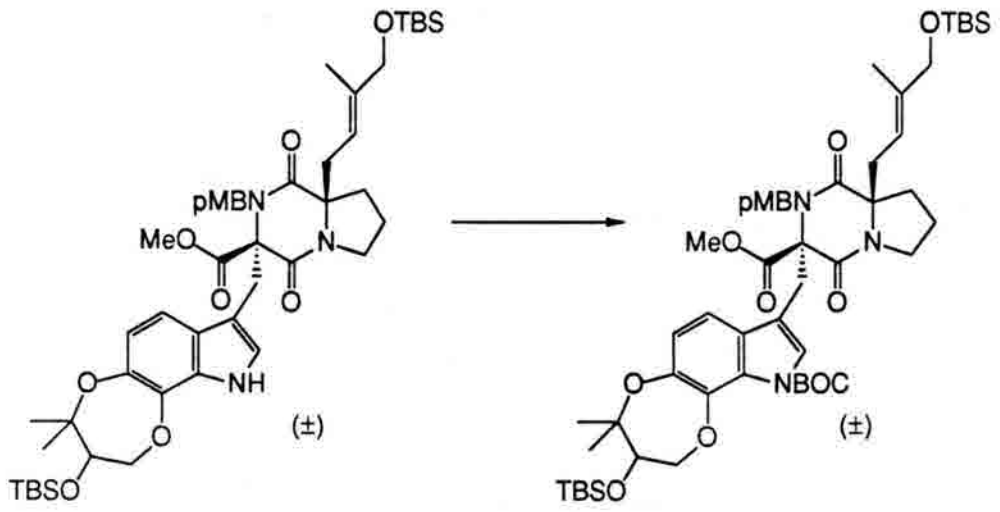
(±)
TBSO
226
INTEGRAL
PPM



223 **228**

[(±)-[3α,8aα(E)]]-1,1-Dimethylethyl-8-[[3-[(methoxy)carbonyl]-2-[(4-methoxyphenyl)methyl]-8a-[4-[[1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (228)

To a stirred solution of the **223** (260.0mg, 0.292mmol, 1.0eq) in CH_2Cl_2 (1.5mL) at 0 °C under Ar was added DMAP (35.7mg, 0.292mmol, 1.0eq) and Et_3N (0.041mL, 0.292mmol, 1.0eq). After 5 min. $(BOC)_2O$ (191.2mg, 0.876mmol, 3.0eq) was added in one portion. The resulting solution was stirred for 20 hours, poured into water and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After concentrating the crude solid was chromatographed. chromatography; radial, 1:5 ethyl acetate/hexane. yield; 260.4mg, 90%.

To a solution of **223** (57.2mg, 0.064mmol, 1.0eq) in THF (0.64mL) at 0 °C was added a THF solution of Potassium t-butoxide (0.11mL, 0.071mmol, 1.1eq, 0.66M). This was followed by a THF solution of t-boc anhydride (0.12mL, 0.071mmol, 1.1eq, 0.59M) 5 minutes later. This mixture was stirred for 20 minutes, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$,

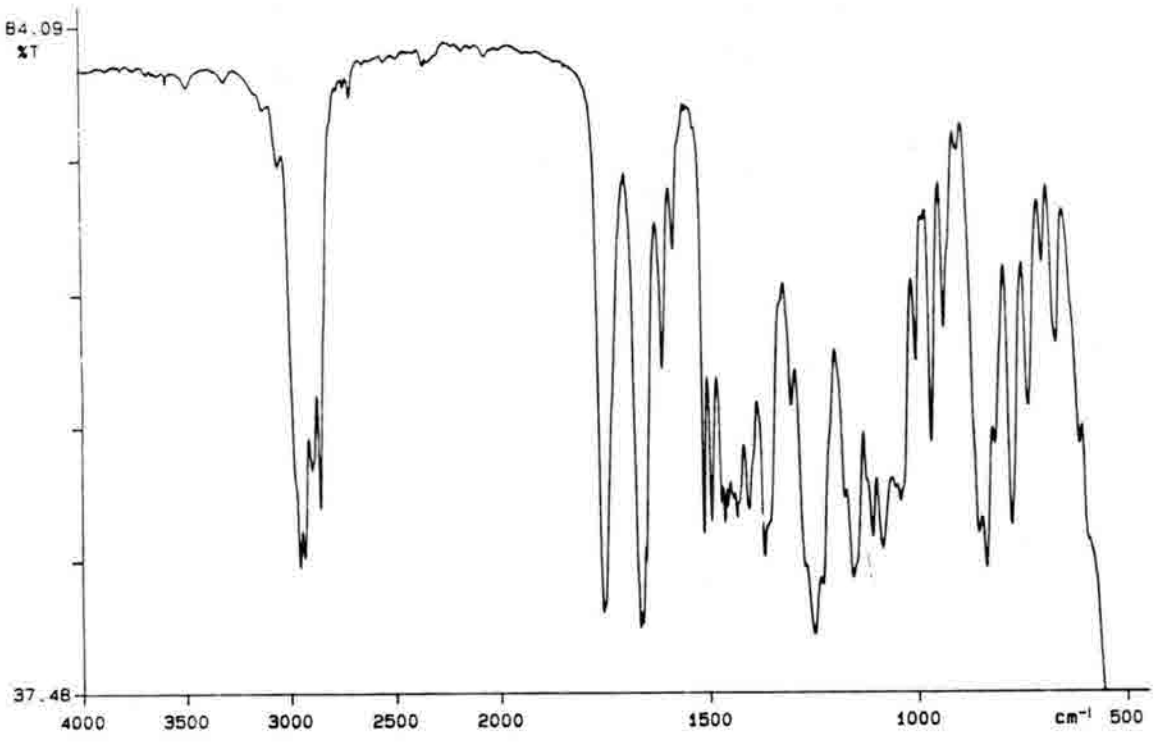
and concentrated. The crude solid was chromatographed. chromatography; (radial) 1:5 ethyl acetate/hexane. yield; 50.1mg, 79%.

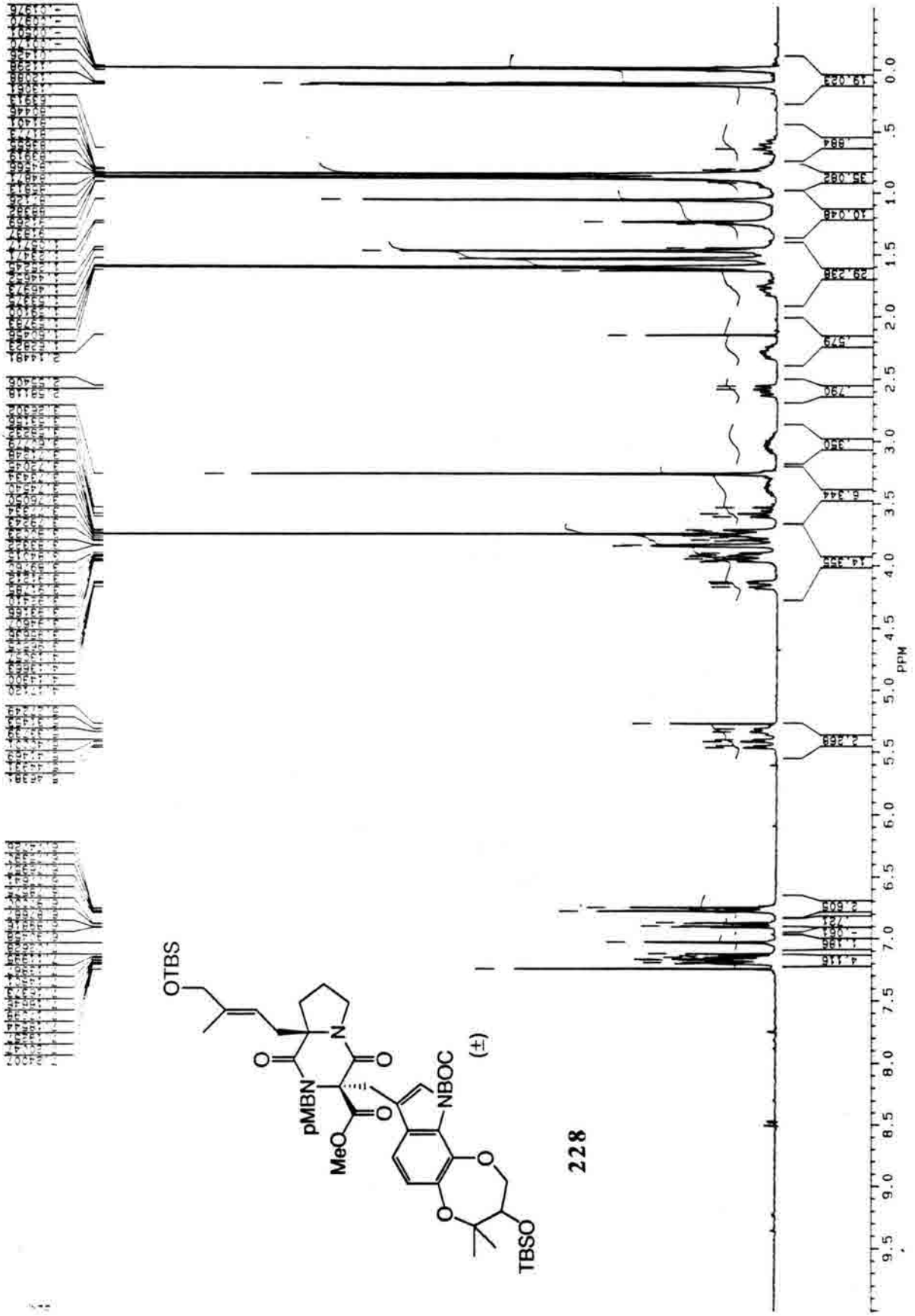
^{1}H NMR (300MHz) ($CDCl_3$) δ –0.01 (6H, s); 0.00 (6H, s); 0.113 (6H, s); 0.12 (6H, s); 0.58–0.68 (2H, m); 0.80–0.92 (38H, m); 1.06 (6H, s); 1.45–1.63 (2H, m); 1.47 (6H, s); 1.53 (6H, s); 1.60 (18H, s); 1.59–1.81 (2H, m); 2.22–2.34 (2H, m); 2.60 (2H, dd, J = 8.1, 15.0Hz); 2.91–3.08 (2H, m); 3.26 (6H, s); 3.26–3.42 (2H, m); 3.56 (1H, ½ ABq, J = 14.8Hz); 3.59 (1H, ½ ABq, J = 14.8Hz); 3.71–3.80 (4H, m); 3.74 (6H, s); 3.83 (2H, s); 3.84 (2H, s); 3.90–3.97 (4H, m); 4.13–4.17 (2H, m); 3.32 (2H, m); 5.34 (1H, ½ ABq, J = 14.8Hz); 5.42 (1H, ½ ABq, J = 14.8Hz); 6.75–6.79 (4H, m); 6.88 (1H, d, J = 8.4Hz); 6.89 (1H, d, J = 8.4Hz); 7.03 (2H, s); 7.12–7.20 (6H, m).

IR (neat) 2943, 1752, 1660, 1507, 1496, 1464, 1463, 1404, 1365, 1251, 1153, 1109, 1082, 837, 772 cm^{-1}.

EI HRMS 989.5249 ($C_{53}H_{79}N_3O_{11}Si_2$ requires 989.5253).

m.p. 74–75 °C, (white crystalline solid).

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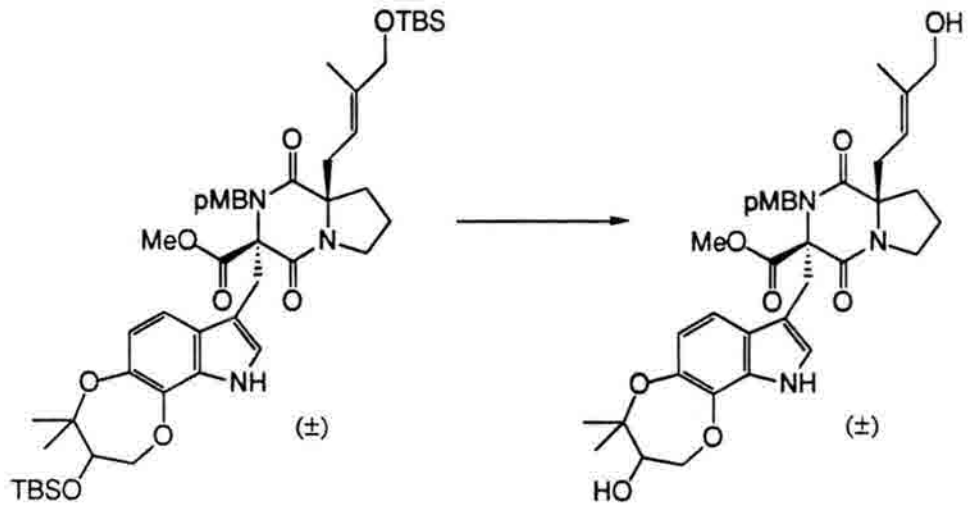
MeO
NBOC
TBSO
(±)
228
PPM



223 **224**

[(±)-[3α,8aα(E)]]-Methyl-3-[[3-hydroxy-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8a-[4-hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxo-pyrrolo[1,2-a]pyrazine-3-carboxylate (224)

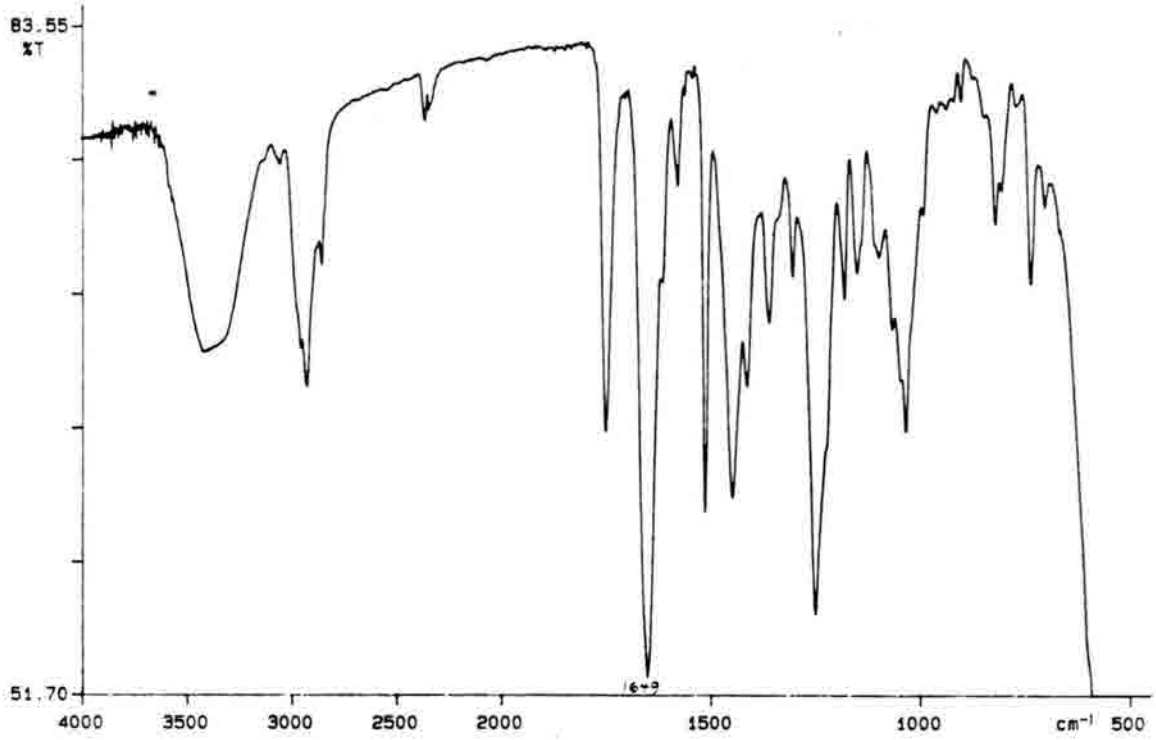
To a stirred solution of **223** (9.6mg, 0.011mmol, 1.0eq) in THF (0.5mL) under N_2 was added n-Bu_4NF (0.026mL, 0.026mmol, 2.4eq,1.0M/THF). The pale yellow solution was placed in an oil bath at 30–42 °C for 6.5h. The mixture was diluted with H_2O and extracted three times with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give 7.6mg of a crude solid. chromatography; (PTLC) ethyl acetate. The product was obtained as a pale yellow glassy foam. yield; 4.8mg, 67%.

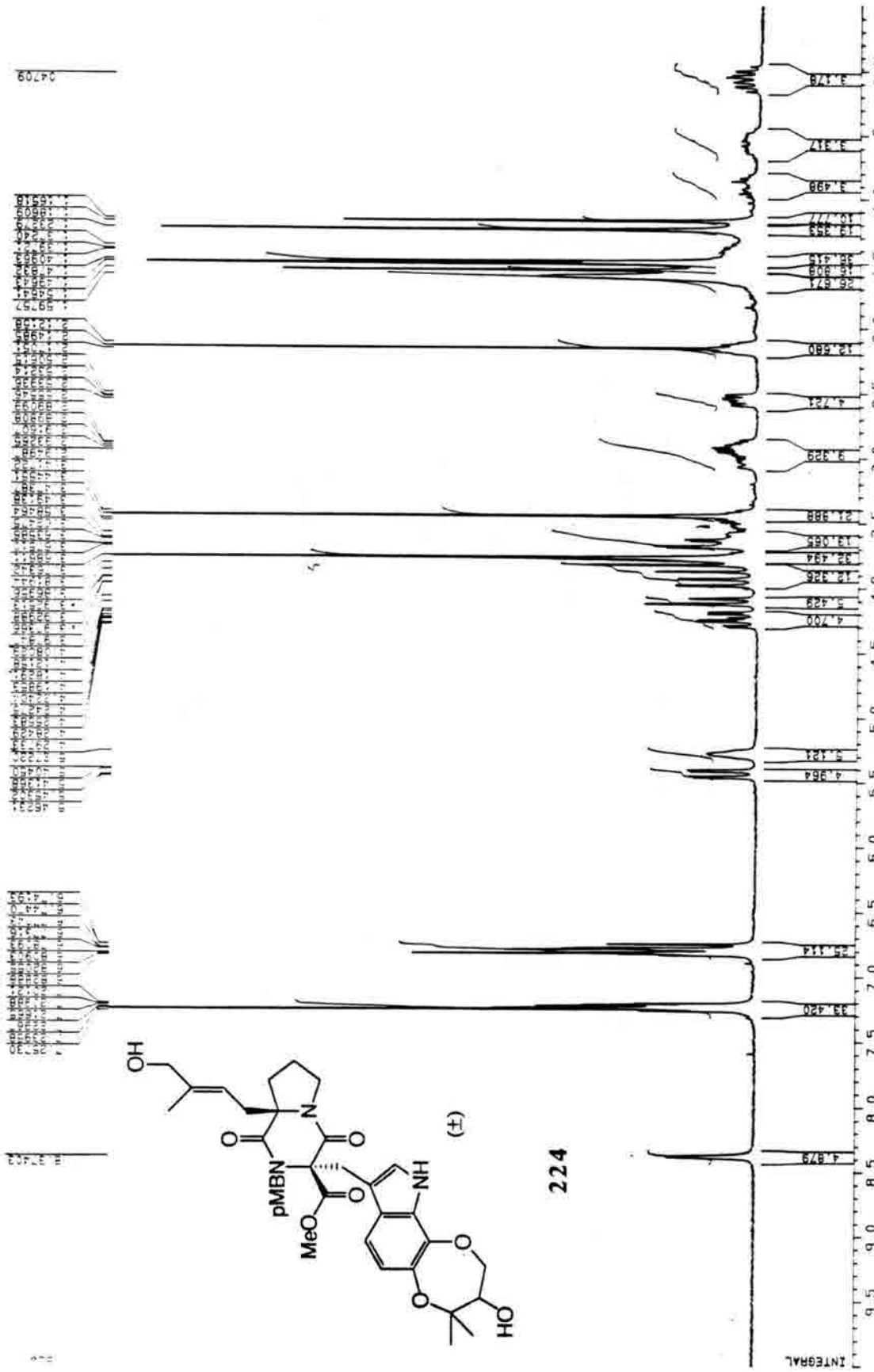
^1H NMR (300MHz) (Acetone-D_6) δTMS 0.10–0.19 (2H, m); 0.51–0.68 (2H, m); 0.85–0.96 (2H, m); 1.25 (3H, s); 1.26 (3H, s); 1.38 (3H, s); 1.39 (3H, s); 1.48–1.54 (2H, m); 1.56 (6H, s); 2.25 (2H, dd, J = 8.0, 15.4Hz); 2.53 (2H, dd, J = 8.0, 15.4Hz); 2.92–3.01 (2H, m); 3.25 (6H, s); 3.45 (4H, m, D_2O exch.); 3.46–3.59 (2H, m); 3.69 (2H, ½ ABq, J = 15.0Hz); 3.76–3.77 (2H, m); 3.78 (2H, ½ ABq, J = 15.0Hz); 3.79 (6H, s); 3.83 (4H, s); 3.91–4.00 (2H, m); 4.12 (2H, ½ ABq, J = 15.1Hz); 4.19–4.27 (2H, m); 5.39–5.43 (2H, m); 5.52 (2H, ½ ABq, J = 15.1Hz); 6.67 (2H, d, J = 8.5Hz); 6.84–6.89

(4H, m); 7.00 (2H, s); 7.15 (2H, d, J = 8.5Hz); 7.20 (4H, d, J = 8.6Hz); 10.21 (2H, br s, D_2O exch.).

^1H NMR (300MHz) ($CDCl_3$) δ –0.098–0.12 (2H, m); 0.48–0.64 (2H, m); 0.81–1.05 (2H, m); 1.23 (6H, s); 1.37–1.40 (2H, m); 1.47 (3H, s); 1.50 (3H, s); 1.55 (6H, s); 2.12–2.19 (2H, m); 2.51–2.56 (2H, m); 2.89–3.15 (4H, m, 2H D_2O exch.); 3.44 (6H, s); 3.42–3.49 (4H, m); 3.58 (2H, br s, D_2O exch.); 3.65 (1H, ½ABq, J = 15.1Hz); 3.66 (1H, ½ABq, J = 15.1Hz); 3.76 (10H, br s); 3.84 (2H, ½ ABq, J = 15.1Hz); 3.94 (1H, ½ ABq, J = 14.6Hz); 3.95 (1H, ½ ABq, J = 14.6Hz); 4.10 (2H, d, J = 12.4Hz); 4.21 (1H, dd, J = 4.5, 12.4Hz); 4.27 (1H, dd, J = 4.5, 12.4Hz); 5.27 (1H, br s); 5.43 (1H, ½ ABq, J = 14.6Hz); 5.44 (1H, ½ ABq, J = 14.6Hz); 6.74–6.83 (8H, m); 7.20–7.26 (6H, m); 8.37 (2H, br s, D_2O exch.).

IR (neat) 3401, 2932, 1747, 1649, 1513, 1447, 1251 cm^{-1}.

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MeO
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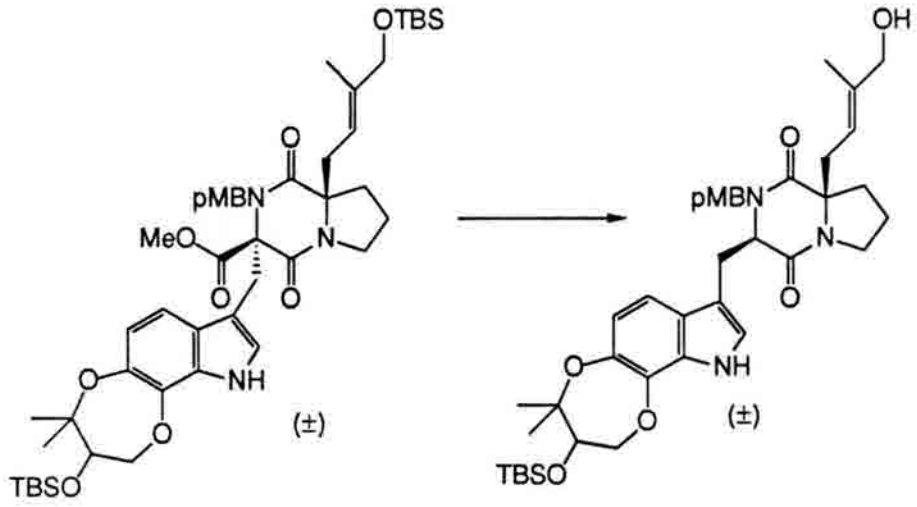
NH
O
O
HO
(±)
224
PPM
INTEGRAL



223 **227**

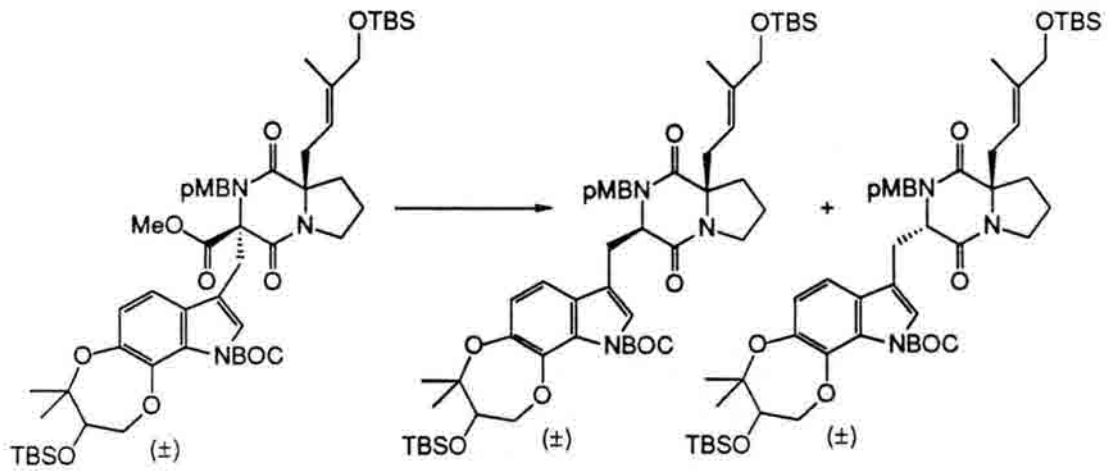
[(±)-[3α,8aα(E)]]-8-[[8a-[4-Hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethyl-silyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole (227)

A small flask containing **223** (21.6mg, 0.024mmol, 1.0eq) and lithium chloride (10.3mg, 0.240mmol, 10.0eq) under N_2 was charged with HMPA (0.2mL) and water ($1.3x10^{-3}$mL, $7.2x10^{-5}$mmol, 3.0eq). This mixture was heated to 100–105 °C for 7h. The resulting solution was diluted with 1:1 ethyl acetate/hexane, washed with water, brine and dried over $MgSO_4$. After concentrating the crude solid was purified. chromatography; (PTLC) 1:1 ethyl acetate/hexane, (white crystalline solid). yield; (*syn)* 10.0mg, 58%.

^1H NMR (300MHz) ($CDCl_3$) (*syn)* δ 0.11 (6H, s); 0.12 (6H, s); 0.86 (9H, s); 0.88 (9H, s); 1.08 (3H, s); 1.12 (3H, s); 1.32–1.40 (1H, m); 1.23 (3H, s); 1.44 (3H, s); 1.47 (3H, s); 1.48 (3H, s); 1.54–1.51 (1H, m); 1.71–1.88 (8H, m, 2H D_2O exch.); 2.04–2.15 (4H, m); 3.16–3.48 (6H, m); 3.57 (2H, d, J = 14.4Hz); 3.69–3.93 (16H, m); 4.14–4.21 (4H, m); 4.76 (1H, m); 5.14 (1H, m); 5.24 (2H, d, J = 14.4Hz); 6.71–6.77 (3H, m); 6.83 (1H, d, J = 2.3Hz); 6.90 (1H, d, J = 2.5Hz); 6.92 (2H, d, J = 8.8Hz); 6.99 (1H, d, J = 8.6Hz); 7.15 (1H, d, J = 8.5Hz); 7.20 (1H, d, J = 8.5Hz); 8.20 (1H, s, D_2O exch.); 8.21 (1H, s, D_2O exch.).

IR (neat) 3379, 2932, 2856, 1649, 1464, 1251, 1088, 837 cm^{-1}.

m.p. 156–157 °C.



228 **229** **230**

[(±)-[3β,8aβ(E)]]-1,1-Dimethylethyl-8-[[8a-[[(1,1-dimethethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl] octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethyl ethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino [2,3-g]indole-10-carboxylate (229)

[(±)-[3α,8aβ(E)]]-1,1-Dimethylethyl-8-[[8a-[[(1,1-dimethethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl] octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethyl ethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino [2,3-g]indole-10-carboxylate (230)

A flask containing **228** (126.6mg, 0.128mmol, 1.0eq) and LiCl (27.1mg, 0.64mmol, 5.0eq) under N_2 was charged with HMPA (0.78mL) and H_2O ($3.4x10^{-3}$mL, $1.9x10^{-4}$mmol, 1.5eq). The solution was heated (100–105 °C) for 1h 15min. and then poured into water and extracted with ether. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated, leaving a crude oily solid. chromatography;

(radial) 1:5 ethyl acetate/hexane. yield; **229** (An analytical sample was obtained by PTLC, 1:5 ethyl acetate/hexane to give an oily foam), 79.2mg, 66%; **230**, 3.1mg, 2.6%.

^{1}H NMR (300MHz) ($CDCl_3$) (**229**) δ 0.026 (6H, s); 0.32 (6H, s); 0.127 (6H, s); 0.14 (6H, s); 0.867 (9H, s); 0.873 (9H, s); 0.878 (9H, s); 0.883 (9H, s); 1.10 (6H, s); 1.48 (3H, s); 1.49 (3H, s); 1.55 (3H, s); 1.57 (3H, s); 1.610 (9H, s); 1.613 (9H, s); 1.83–1.96 (6H, s); 2.22–2.35 (4H, m); 2.46 (2H, dd, J = 6.0, 15.0Hz); 3.11–3.21 (2H, m); 3.31–3.85 (2H, m); 3.37 (1H, ½ABq, J = 14.5Hz); 3.48 (1H, ½ABq, J = 14.6Hz); 3.71 (3H, s); 3.72 (3H, s); 3.76–3.98 (8H, m); 3.99 (2H, m); 4.02 (2H, s); 4.15–4.21 (4H, m); 5.17 (1H, ½ABq, J = 14.5Hz); 5.20 (1H, ½ABq, J = 14.6Hz);5.35 (1H, m); 5.48 (1H, m); 6.62–6.70 (6H, m); 6.79 (2H, m); 6.91 (2H, d, J = 8.3Hz); 7.14 (1H, d, J = 8.4Hz); 7.16 (1H, d, J = 8.3Hz); 7.22 (1H, s); 7.23 (1H, s).

IR (neat) *(syn)* 2932, 1755, 1661, 1455, 1367, 1250, 1156, 1114,1091, 838 cm^{-1}.

EI HRMS *(syn)* 931.51955 ($C_{51}H_{77}N_3O_9Si_2$ requires 931.5198)

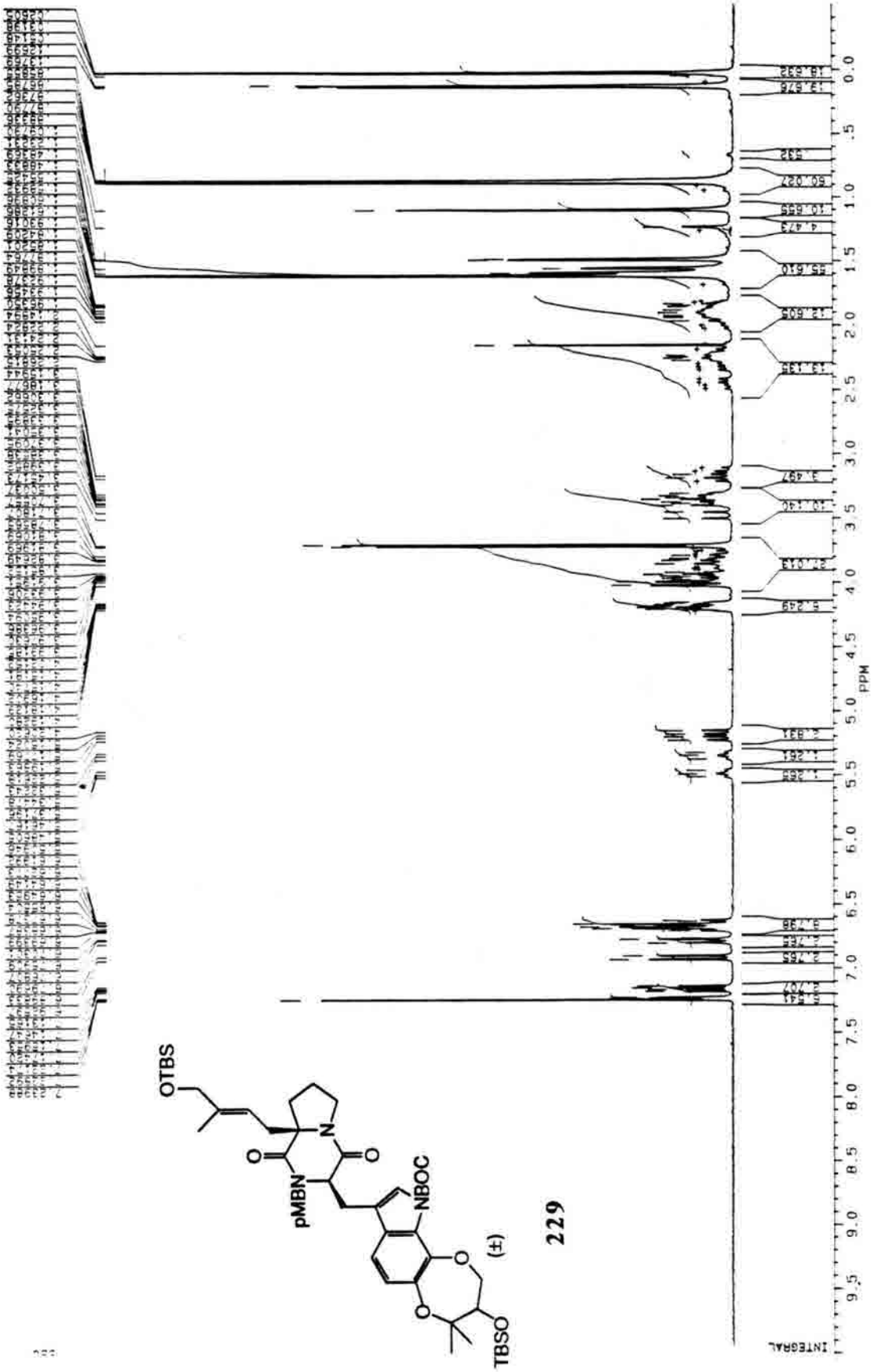
microanalysis calc'd. for $C_{51}H_{77}N_3O_9Si_2$: C, 65.70; H, 8.32; N, 4.51 found: C, 65.37; H, 8.37; N, 4.54.

m.p. oil.

^{1}H NMR (300MHz) ($CDCl_3$) (**230**) δ –0.02 (6H, s); –0.01 (6H, s); 0.03–0.22 (2H, m); 0.12 (6H, s); 0.13 (6H, s); 0.146–0.62 (4H, m); 0.84 (9H, s); 0.85 (9H, s); 0.87 (18h, s); 1.05 (3H, s); 1.07 (3H, s); 1.43 (3H, s); 1.47 (3H, s); 1.49 (3H, s); 1.52 (3H, s); 1.55 (9H, s); 1.60 (9H, s); 1.80–1.91 (2H, m); 2.19–2.22 (2H, m); 2.50–2.61 (2H, m); 3.09–3.23 (2H, m); 3.29–3.52 (4H, m); 3.63–3.96 (18H, m); 4.13–4.20 (4H, m); 5.04–5.10 (1H, m); 5.28–5.32 (1H, m); 5.48 (1H, ½ABq, J = 14.3Hz); 5.52 (1H, ½ABq, J = 14.3Hz); 6.71–6.90 (3H, m); 7.04–7.22 (4H, m).

IR (neat) *(anti)* 3295 (br), 1753, 1657, 1510, 1447, 1249, 1152, 1090, 1034, 836, 773 cm^{-1}.

m.p. oil.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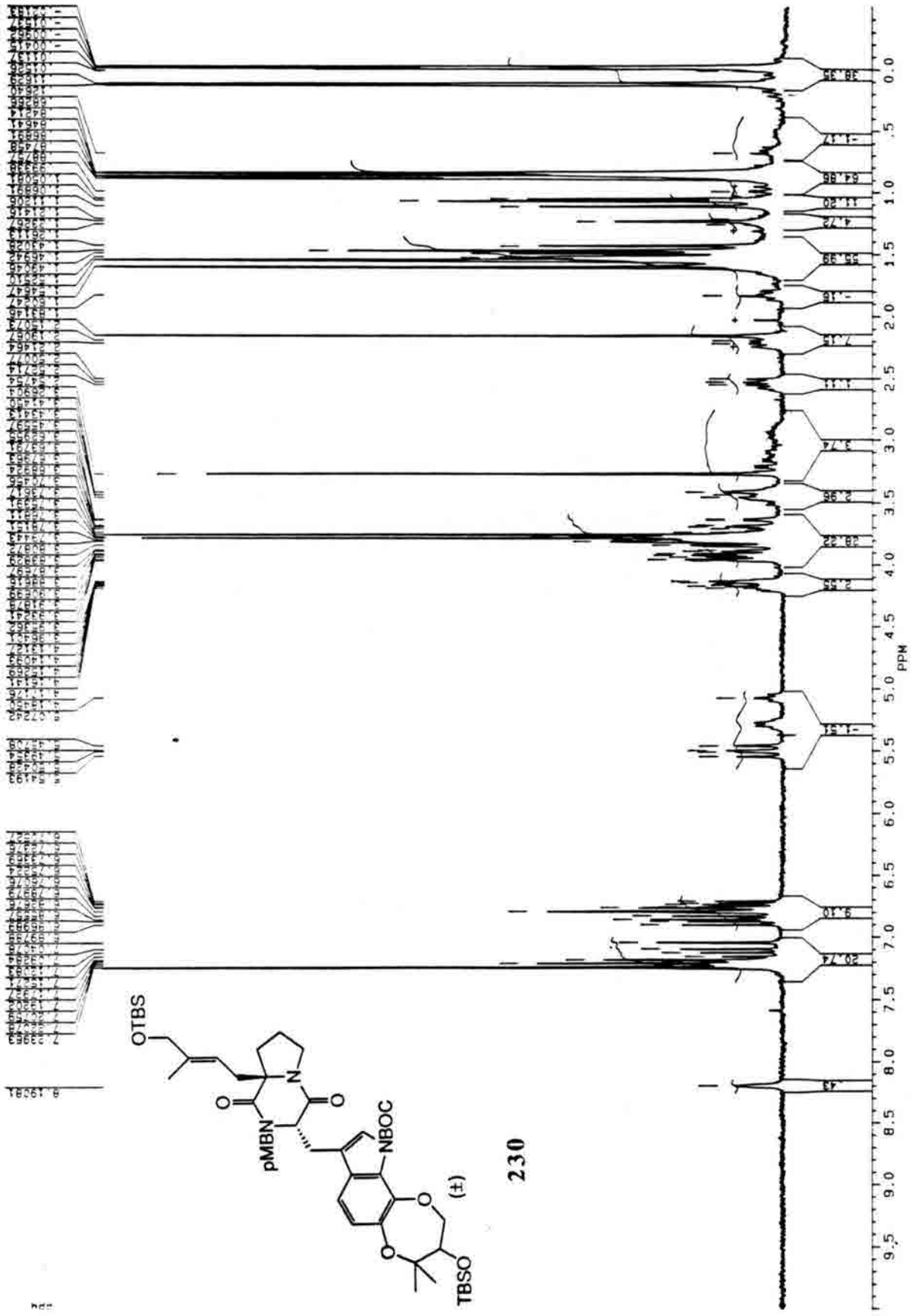
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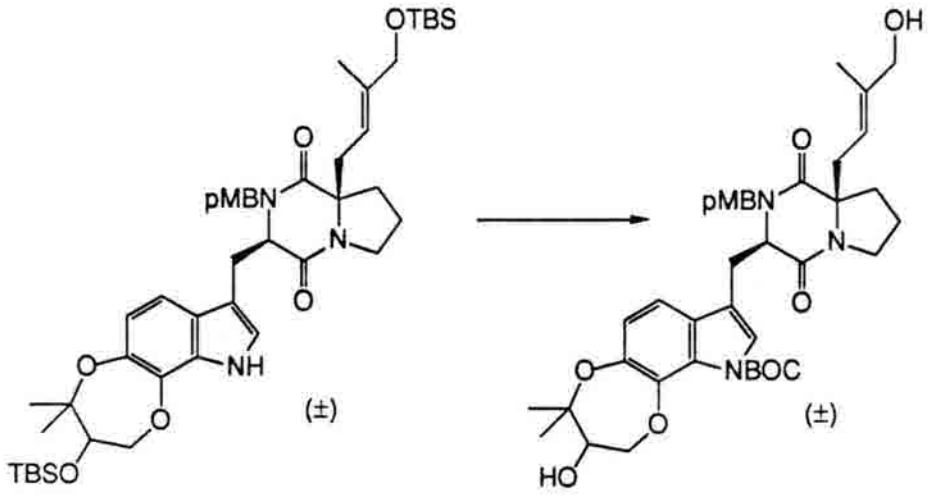


225 **231**

1,1-Dimethylethyl-8-[[8a-[4-hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-hydroxy-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (231)

To a stirred solution of **225** (58.8mg, 0.071mmol, 1.0eq) in THF (1.0mL) at 0 °C, under N_2 was added potassium t-butoxide (0.15mL, 0.78mmol, 1.0eq, 0.59M/THF). This was followed by t-Boc anhydride (0.13mL, 0.078mmol, 1.0eq, 0.59M/THF) ten minutes later. In approximately 2 hours an additional amount of t-Boc anhydride (1.0eq) was added which was followed by potassium t-butoxide (0.5eq) after another 2 hours. One half hour later the reaction was complete by TLC. At this time a solution of n-Bu_4NF (0.36mL, 0.36mmol, 5.0eq) was syringed into the flask at room temperature. This was allowed to stir overnight. The solution was then diluted with ethyl acetate washed with H_2O, brine and dried over magnesium sulfate. After solvent removal, an oily crude product was obtained. chromatography; radial, ethyl acetate, (foamy solid). yield; 45.3mg, 91%.

^1H NMR (300MHz) ($CDCl_3$) δ 1.19 (3H, s); 1.22 (3H, s); 1.52 (3H, s); 1.53 (3H, s); 1.56 (3H, s); 1.57 (3H, s); 1.59 (9H, s); 1.60 (9H, s); 1.72–2.21 (12H, m); 2.71 (2H, br

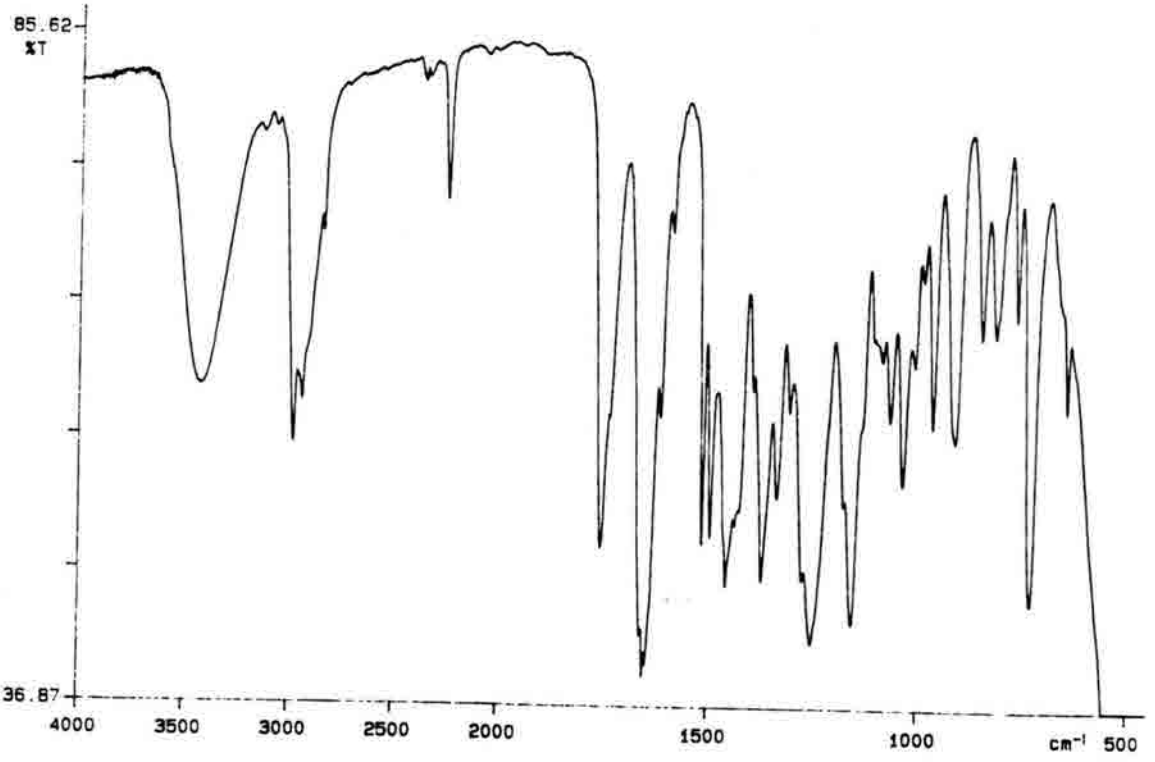
s, D_2O exch.); 3.18–3.49 (3H, m); 3.51 (2H, ½ ABq, J = 14.5Hz); 3.56 (1H, s, D_2O exch.); 3.61 (1H, s, D_2O exch.);

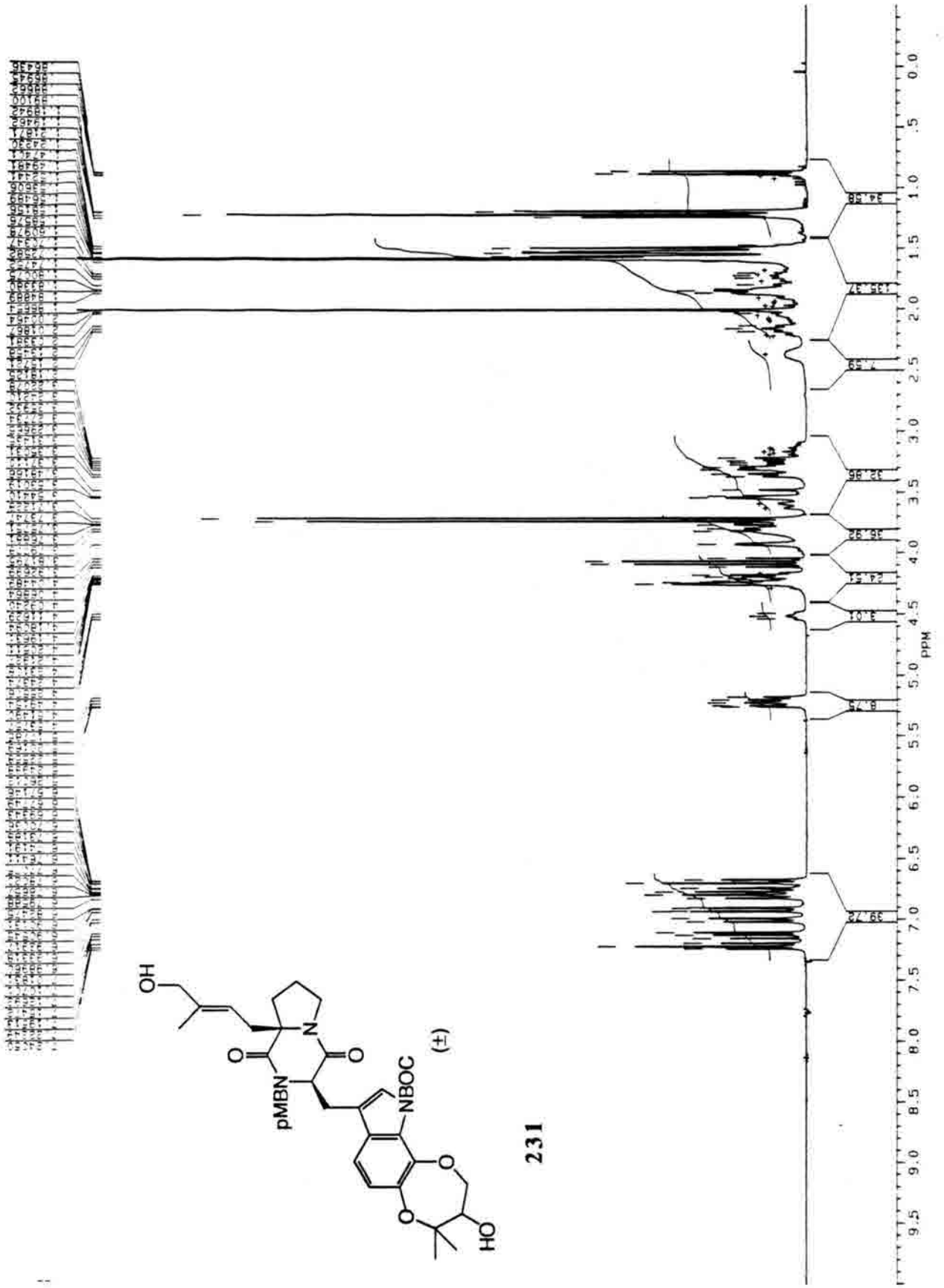
3.72 (3H, s); 3.74 (3H, s); 3.75–3.94 (6H, s); 4.18–4.30 (3H, s); 4.26 (2H, s); 4.27 (2H, s); 4.44 (1H, m); 5.25 (1H, ½ ABq, J = 14.5Hz); 5.25 (1H, ½ ABq, J = 14.4Hz); 6.70 (1H, d, J = 8.7Hz); 6.77 (1H, d, J = 8.6Hz); 6.83 (1H, d, J = 8.6Hz); 6.927 (1H, d, J = 8.4Hz); 6.932 (1H, d, J = 8.3Hz); 7.03 (1H, d, J = 8.6Hz); 7.12 (1H, d, J = 8.3Hz); 7.15 (1H, d, J = 8.4Hz); 7.21 (1H, s); 7.23 (1H, s).

IR (neat) 3422, 2976, 1753, 1649, 1513, 1496, 1457, 1371, 1333, 1251, 1153, 1033, 733 cm^{-1}.

MS (EI) m/e 703 relative intensity 703 (M^+, 8) 604 (37) 603 (100).

EI HRMS 703.3461 ($C_{39}H_{49}N_3O_9$ requires 703.3472).





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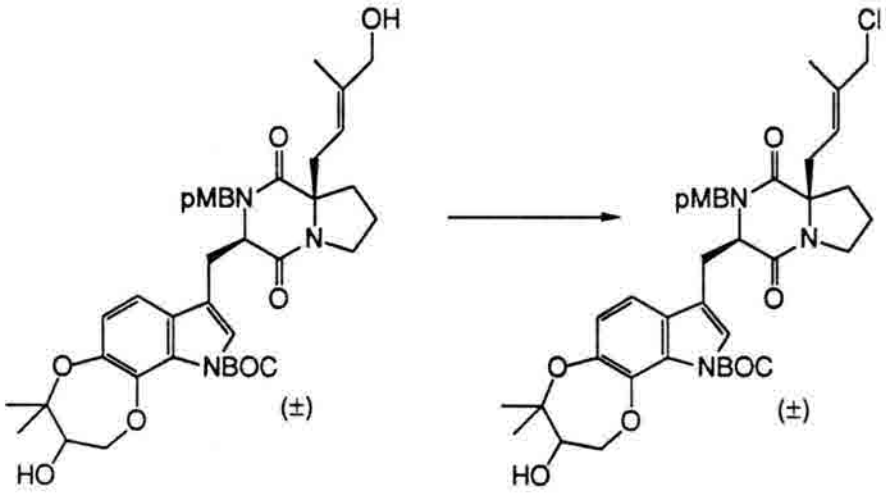


231 **232**

1,1-Dimethylethyl-8-[[8a-[4-chloro-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-hydroxy-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (232)

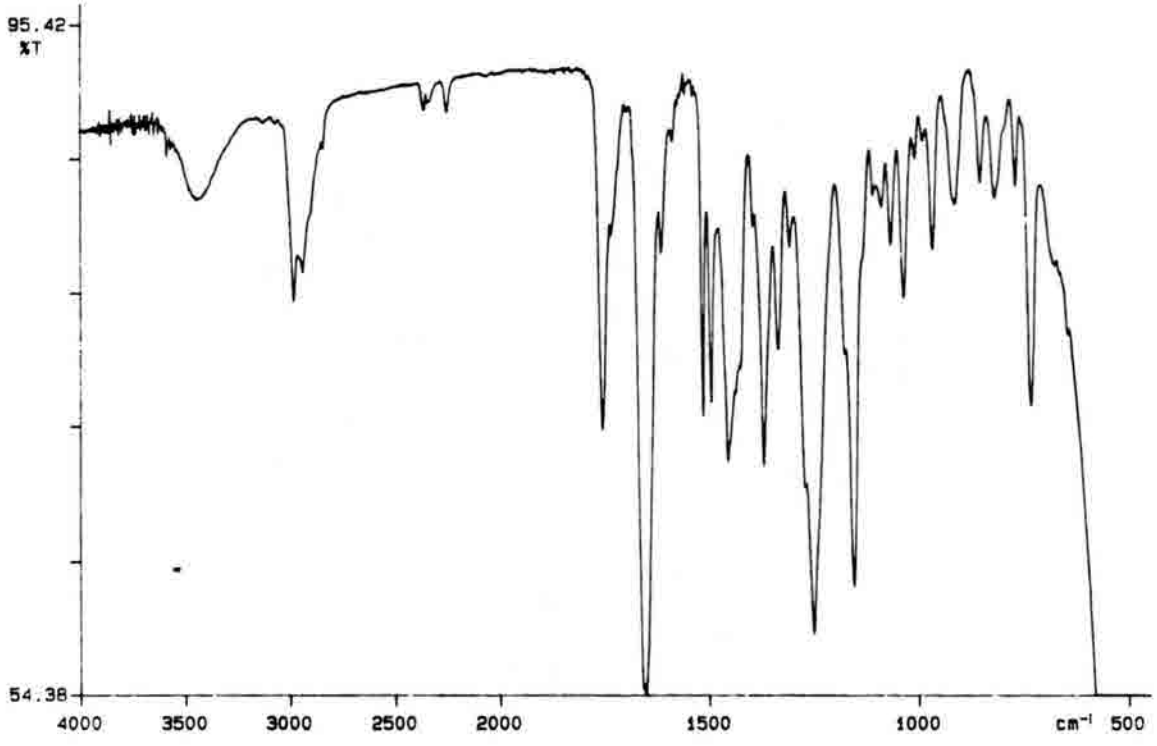
To **231** (24.9mg, 0.035mmol, 1.0eq) in DMF (0.35mL) at 0 °C under Ar was added dry LiCl (2.9mg, 0.068mmol, 1.9eq) and collidine (0.007mL, 0.053, 1.5eq). After stirring for ten minutes methane sulfonylchloride (0.004mL, 0.053mmol, 1.5eq) was added dropwise. The mixture was allowed to reach room temperature in the course of 24 hours. At this time an additional amount of collidine (2.5eq) and methane sulfonylchloride (2.5eq) was added and stirred for two more hours. It was then diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$, and concentrated to dryness. chromatography; PTLC, 2:1 ethyl acetate/hexane, yield; 21.9mg, 86%.

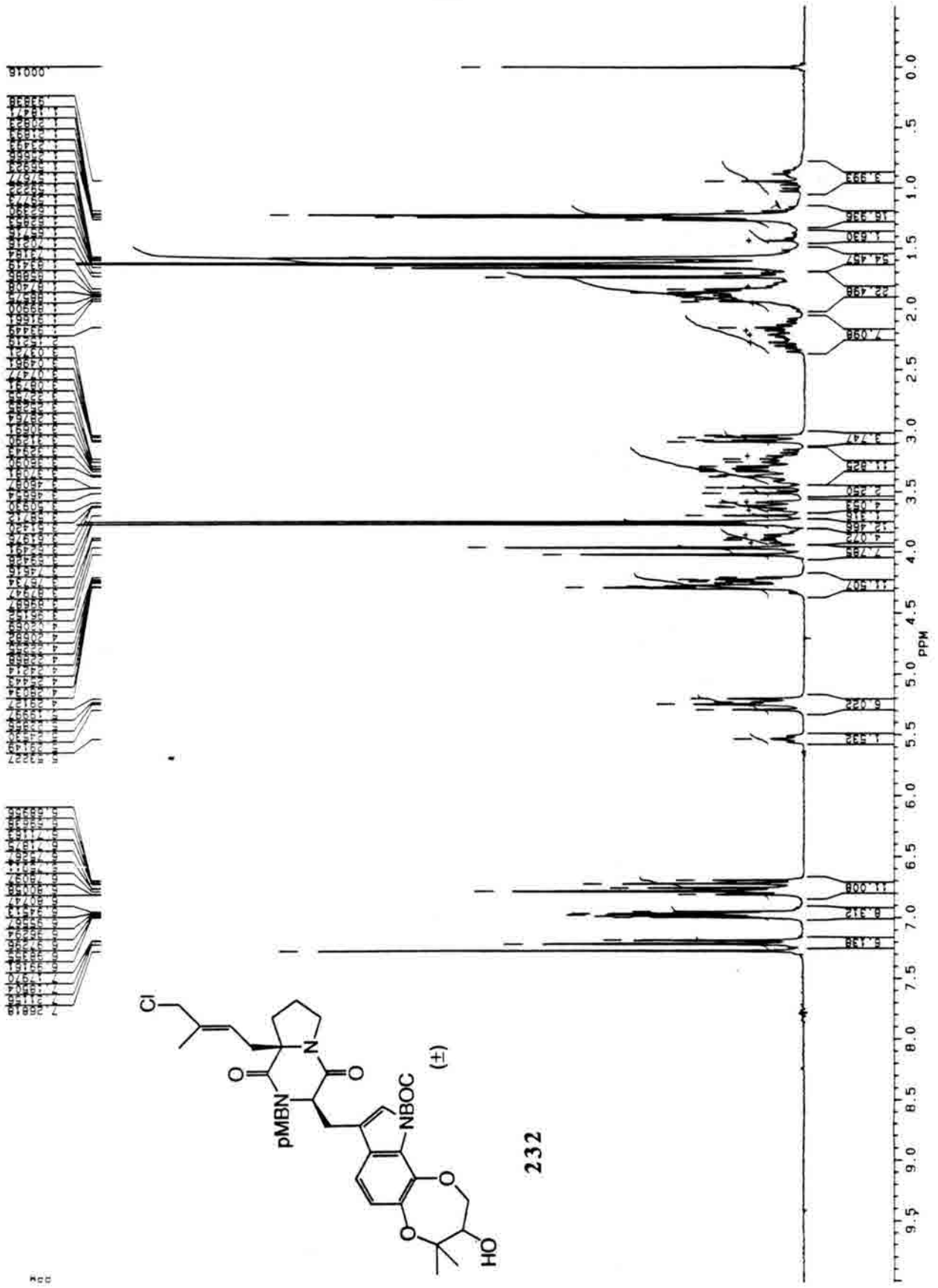
^1H NMR (300MHz) ($CDCl_3$) δTMS 1.22 (3H, s); 1.23 (3H, s); 1.57 (3H, s); 1.58 (3H, s); 1.62 (9H, s); 1.63 (9H, s); 1.66 (3H, s); 1.73 (3H, s); 1.83–1.93 (8H, m); 2.05–2.37 (4H, m); 3.06 (2H, dd, J = 3.8, 11.4Hz); 3.35–3.42 (6H, m, 1H D_2O exch.); 3.46–3.69 (4H, m); 3.75 (3H, s); 3.77 (3H, s); 3.86–3.94 (2H, m); 3.96 (2H, s); 4.02 (2H, s);

4.21–4.29 (6H, m); 5.20–5.29 (3H, m); 5.53 (1H, m); 6.69–6.81 (6H, m); 6.94–6.99 (4H, m); 7.18–7.21 (4H, m).

IR (neat) 3433, 2976, 1752, 1654, 1513, 1496, 1453, 1371, 1251, 1153 cm^{-1}.

m.p. oil.

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(±)
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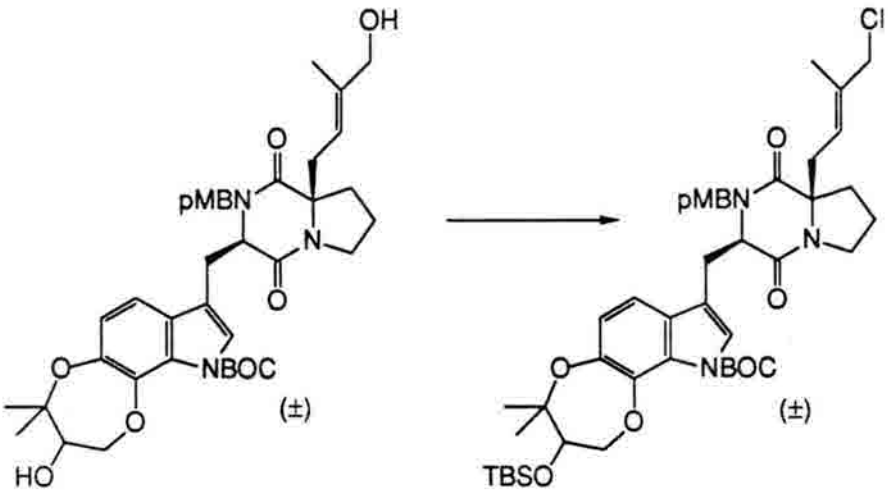
232
PPM



232 **234**

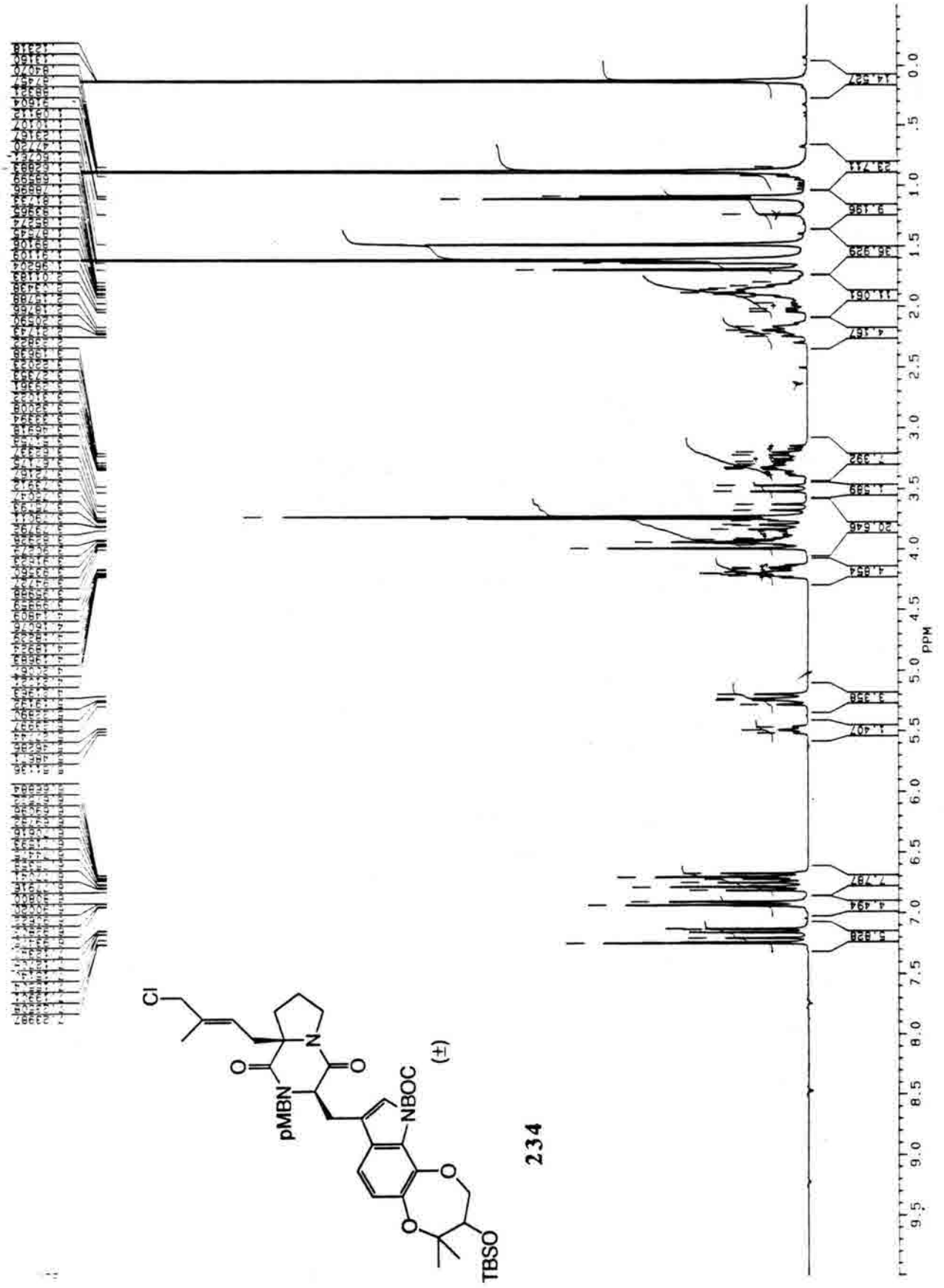
1,1-Dimethylethyl-8-[[8a-[4-hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (234)

To a solution of **234** (28.2mg, 0.0391mmol, 1.0eq) in CH_2Cl_2 (0.3mL) at 0 °C under Ar was added t-BDMSOTf ($9.0x10^{-3}$mL, 0.041mmol, 1.2eq) followed immediatly by 2,6-lutidine ($6.0x10^{-3}$mL, 0.047mmol, 1.4eq). It was stirred for 2 hours, then diluted with ethyl acetate, washed with water, brine and dried over $MgSO_4$ and concentrated. chromatography; radial, 1:1 ethyl acetate/hexane, yield; 24.9mg, 76%.

^{1}H NMR (300MHz) ($CDCl_3$) δ 0.12 (6H, s); 0.13 (6H, s); 0.87 (9H, s); 0.88 (9H, s); 1.08 (3H, s); 1.10 (3H, s); 1.48 (6H, s); 1.61 (9H, s); 1.63 (9H, s); 1.69 (3H, s); 1.79 (3H, s); 1.82–2.03 (8H, m); 2.16–2.24 (4H, m); 3.19 (2H, dd, J = 7.2, 8.5Hz); 3.25–3.39 (4H, m); 3.49 (1H, ½ ABq, J = 14.5Hz); 3.65 (1H, ½ ABq, J = 14.5Hz); 3.72 (3H, s); 3.76 (3H, s); 3.79–3.99 (8H, m); 4.15–4.22 (4H, m); 5.19–5.28 (4H, m); 5.49 (2H, m); 6.67–6.81 (6H, m); 6.92 (4H, dd, J = 1.9, 8.4Hz); 7.13 (1H, d, J = 8.4Hz); 7.14 (1H, d, J = 8.4Hz); 7.20 (1H, s); 7.24 (1H, s).

IR (neat) 2932, 1752, 1654, 1512, 1491, 1447, 1365, 1251, 1153, 1088, 837 cm^{-1}.

m.p. oil.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7.787
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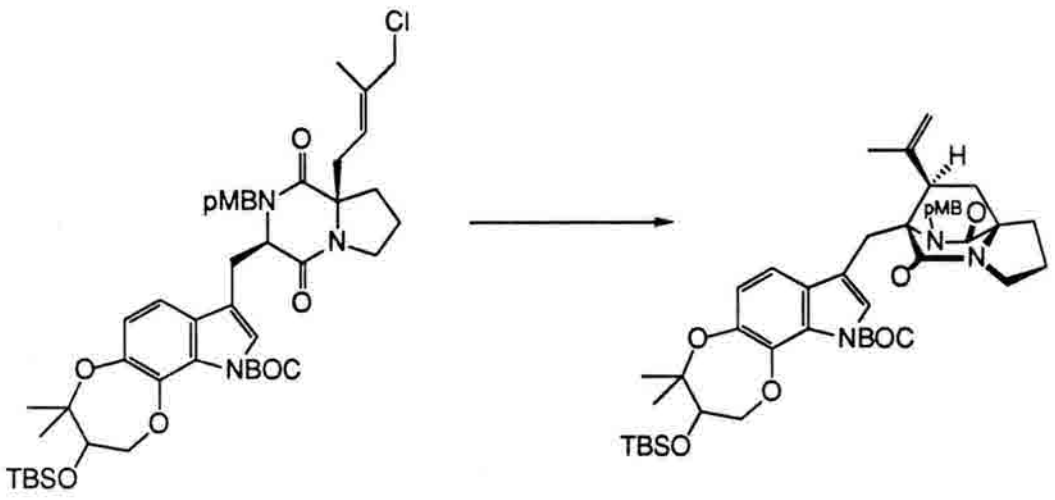
PPM

234



234 **235**

[(±)-[3α,8aα10(R*)]]-1,1-Dimethylethyl-8-[[tetrahydro-2-[(4-methoxyphenyl)methyl]-10-(1-methylethenyl)-1,4-dioxo-6*H*-3,8a-ethanopyrolo[1,2-a]pyrazin-3(4H)-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino-[2,3-g]-indole-10-carboxylate (235)

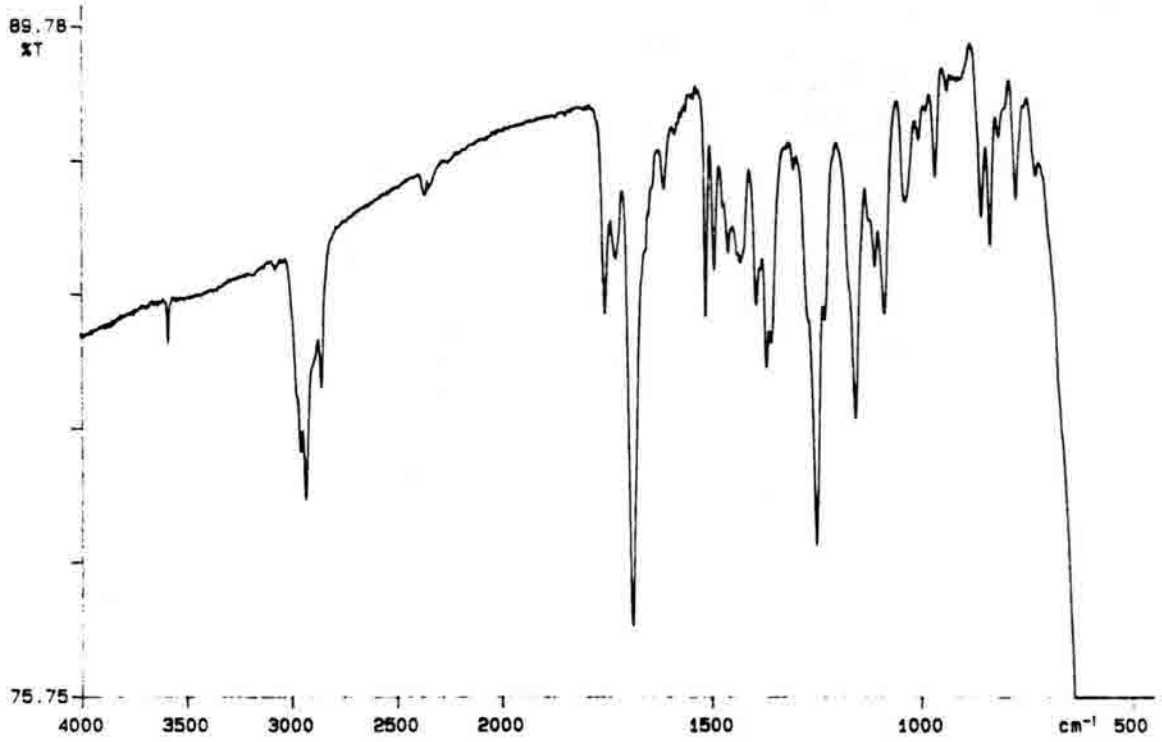
To **234** (24.0mg, 0.0287mmol, 1.0eq) in a flask with a magnetic stir bar was added NaH (12.3mg, 0.310mmol, 10.8eq) and benzene (3.5mL). The flask was fitted with a condenser and gently refluxed for 59 hours (an additional amount of benzene (1.5mL) was added during this time). The solution was stirred at room temperature for 8 days after which NaI (10,8eq, 0.072mmol, 2.5eq) was added. The mixture was then refluxed an additional 2 days. The resulting mixture was diluted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, and concentrated. chromatography; PTLC, 1:1 hexane/ethyl acetate, (The product was obtained as an amorphous yellow solid). yield 2.5mg, 11%.

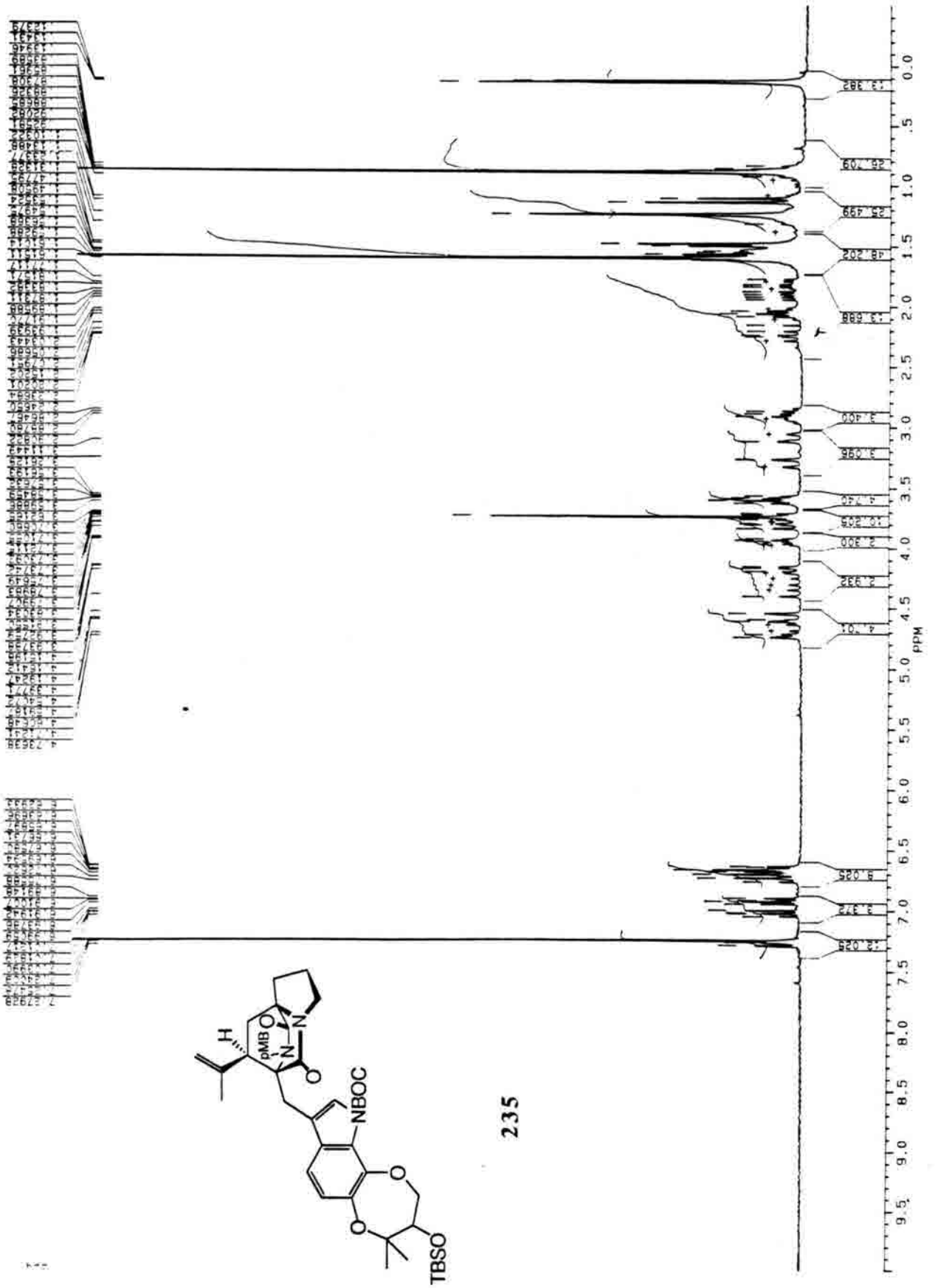
^{1}H NMR (300MHz) ($CDCl_3$) δ 0.12 (3H, s); 0.14 (3H, s); 0.882 (9H, s); 0.885 (9H, s); 1.10 (3H, s); 1.13 (3H, s); 1.48 (3H, s); 1.49 (3H, s); 1.55 (3H, s); 1.56 (3H, s); 1.59 (18H, s); 1.80 (2H, dd, J = 5.7, 13.3Hz); 1.90 (2H, dd, J = 13.2Hz); 2.03–2.08 (4H, m); 2.22 (2H, dd, J = 10.4, 13.4Hz); 2.85–2.98 (4H, m); 3.08 (2H, ½ ABq, J =

17.1Hz); 3.29 (2H, ½ ABq, J = 17.6Hz); 3.56–3.62 (4H, m); 3.72 (3H, s); 3.73 (3H, s); 3.74–3.83 (2H, dd, J = 9.4, 12.5Hz); 3.91–3.96 (2H, m); 4.18 (2H, dd, J = 3.6, 12.2Hz); 4.28 (1H, ½ABq, J = 15.9Hz); 4.37 (1H, ½ ABq, J = 15.9Hz); 4.54–4.74 (6H, m); 6.62–6.75 (8H, m); 6.89–6.94 (2H, m); 6.99–7.04 (2H, m); 7.25 (1H, s); 7.28 (1H, s).

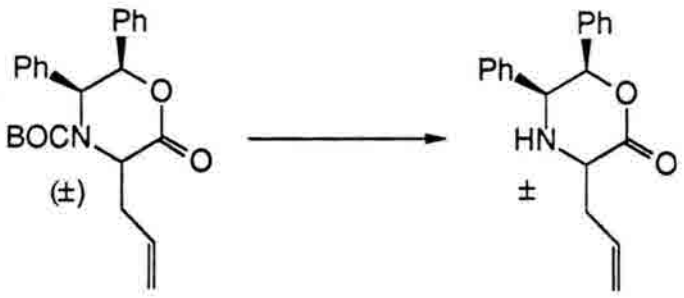
IR (neat) 2932, 1687, 1365, 1251, 1158, 1088 cm^{-1}.

EI HRMS 799.4252 ($C_{45}H_{61}N_3O_8Si$ requires 799.4228).





235

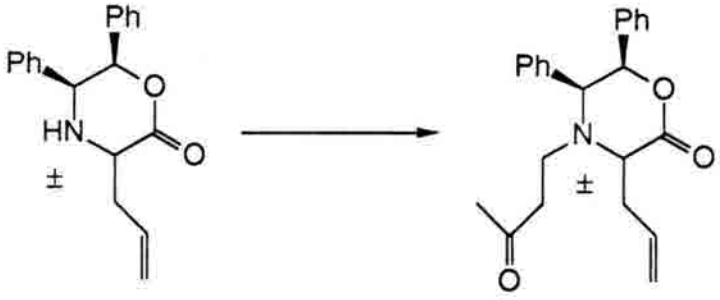


247 **248**

To a stirred solution of **247** (53.2mg, 0.135mmol, 1.0eq) in CH_2Cl_2 (4.0mL) at room temperature, under Ar was added trifluoroacetic acid (0.21mL, 2.7mmol, 20.0eq). After 20 hours the solvent was removed. The residue was dried and recharged with CH_2Cl_2 (4.0mL) and Et_3N (0.06mL, 0.45mmol, 3.3eq). This was stirred for 20 minutes and then evaporated to dryness, (oil). yield; 27.9mg, 70%.

^1H NMR (300MHz) ($CDCl_3$) δTMS 1.55 (1H, s, D_2O exch.); 2.71–2.78 (2H, m); 4.03 (1H, ABq, J = 4.6, 8.4Hz); 4.69 (1H, d, J = 3.6Hz); 5.10–5.17 (2H, m); 5.6591H, d, J = 3.7Hz); 5.78–5.82 (1H, m); 6.87–6.90 (2H, m); 6.94–6.98 (2H, m); 7.12–7.20 (6H, m).

IR (neat) 3324, 2925, 1736, 1640, 1378, 1198, 913, 699 cm^{-1}.



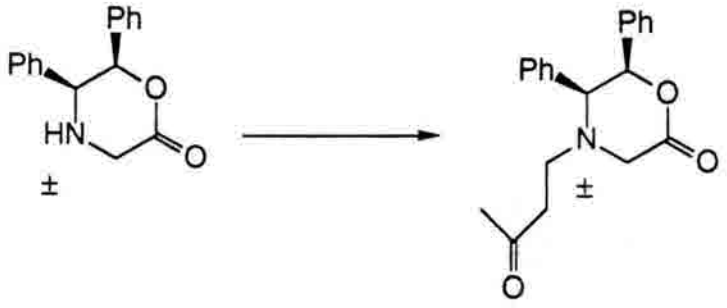
248 **249**

To a stirred solution of **248** (27.9mg, 0.095mmol, 1.0eq) in diethyl ether (0.5mL) THF (0.5mL) and t-butanol (0.053mL) was added potassium t-butoxide (1.7mg, 0.15mmol, 0.16eq) at room temperature, under Ar. To this was added methyl vinyl ketone (0.024mL, 0.285mmol, 3.0eq) dropwise. The mixture was stirred for three days, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine,

dried over $MgSO_4$, and concentrated to dryness, (white solid). chromatography; PTLC, 3:2, hexane/ethyl acetate, yield; 5.5mg, 14%.

^1H NMR (300MHz) ($CDCl_3$) δTMS 2.13 (3H, d, J = 8.0Hz); 2.52 (2H, t, J = 6.8Hz); 2.69–2.80 (3H, m); 2.92–2.97 (1H, m); 3.97 (1H, m); 4.20 (1H, d, J = 3.0Hz); 5.19–6.07 (1H, m); 6.73–6.76 (2H, m); 6.96–6.99 (2H, m); 7.08–7.16 (6H, m).

IR (neat) 2916, 1742, 1721, 1455, 1358, 1256, 1138, 1066, 923 cm^{-1}.



237 **246**

To **237** (100.1mg, 0.395mmol, 1.0eq) in a mixture solvents; diethyl ether (1.4mL) THF (1.0mL) and t-butanol (0.22mL) was added potassium t-butoxide (5.1mg, 0.045mmol, 0.12eq). This was followed by the dropwise addition of methyl vinyl ketone (0.1mL, 1.2mmol, 3.0eq). The mixture was stirred at room temperature for 3 days, diluted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, and concentrated to dryness, (white solid). yield; 107.4mg, 84%.

^1H NMR (300MHz) ($CDCl_3$) δTMS 2.0593H, s); 2.56 (2H, m); 3.70 (2H, s); 4.11 (1H, d, J = 4.0Hz); 5.76 (1H, d, J = 4.0Hz); 6.85–6.87 (2H, m); 7.00–7.02 (2H, m);l 7.11–7.16 (6H, m).

IR (neat) 2921, 1747, 1714, 1496, 1453, 1360, 1273, 1126, 1055, 701 cm^{-1}.

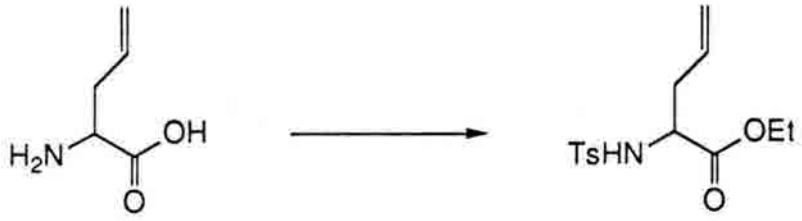
245

N-Benzoxycarbonyl-glycine ethyl ester (245)

To a solution of glycine ethyl ester hydrochloride (670.5mg, 4.80mmol, 1.0eq) in water (10mL) was added Na_2CO_3 (1.53g, 14.4mmol, 3.0eq) followed by benzyl chloroformate (0.75mL, 5.28mmol, 1.1eq) at 0 °C under Ar. The solution was stirred overnight, acidified, pH = 7, and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated, (white solid). yield; 830.2mg, 82%.

^1H NMR (300MHz) ($CDCl_3$) δTMS 1.28 (3H, t, J = 7.1 Hz); 3.9892H, d, J = 5.5Hz); 4.22 (2H, q, J = 7.1, 14.3Hz); 5.13 (2H, s); 5.25 (1H,s, D_2O exch.); 7.31–7.37 (5H, m).

IR (neat) 3354, 1725, 1522, 1276, 1202, 1054, 1027, 698 cm^{-1}.



243

D,L, Ethyl-N-tosyl-2-amino,4-pentenoate (243)

To a stirred suspension of D,L,2-amino,4-pentenoic acid (1.025g, 8.90mmol, 1.0eq) in ethanol (7.1mL) at 0 °C, under Ar was added thionyl chloride (0.65mL, 8.90mmol, 1.0eq) dropwise. After 11 hours diethyl ether was added, stirred a few moments, and then the whole mixture reduced to dryness. The crude mass (1.9g) was taken up in water (18.4mL) and THF (1.4mL) and was subjected to Na_2CO_3 (2.44g, 22.18mmol, 2.5eq). After stirring under Ar for a few minutes Toluenesulfonylchloride (1.86g, 9,76mmol, 1.1eq) was added. One day later the mixture was diluted with water

and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. chromatography; radial, 1:3 ethyl acetate/hexane, yield;.75mg, 66%.

^1H NMR (300MHz) ($CDCl_3$) δTMS 1.10 (3H, t, J = 6.0Hz); 2.43 (3H, s); 2.50 (2H, m); 4.01 (3H, m); 5.12 (3H, m); 5.39 (1H, s, D_2O exch.); 5.69 (1H, m); 7.30 (2H, d, J = 12.0Hz); 7.73 (2H, d, J = 12.0Hz).

238 **239**

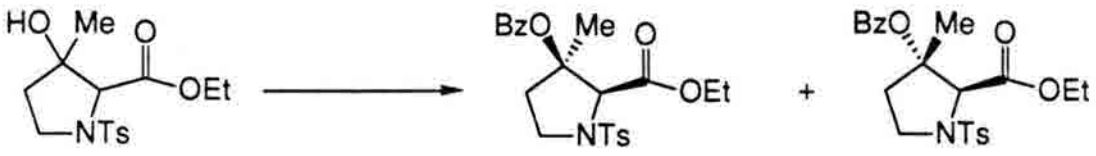
Ethyl 3(RS)-hydroxy-3-methyl-1-toluene-p-sulfonylpyrrolidine-2-(RS)-carboxylate (239)

To a stirred solution of **238** (54.2mg, 0.212mmol, 1.0eq) in t-butanol (0.37mL) and diethyl ether (0.76mL) under Ar, was added potassium t-butoxide (1.7mg, 0.015mmol, 0.07mmol). After a few minutes methyl vinyl ketone (0.53mL, 0.63mmol,3.0eq) was added dropwise. The resulting solution was stirred 3 days, diluted with ethyl acetate, washed with dilute HCl, water, brine, dried over $MgSO_4$, and concentrated to dryness, (white solid). yield; 62.1mg, 98%.

^1H NMR (300MHz) ($CDCl_3$) (mixture of diastereomers) δTMS 1.20–1.31 (12H, m); 1.68–1.78 (1H, m); 1.82–1.90 (1H, m); 1.99–2.18 (2H, m); 2.34 (1H, s, D_2O exch.); 2.41 (3H, s); 2.43 (3H, s); 2.79 (1H, s, D_2O exch.); 3.44–3.49 (2H, m); 3.55–3.63 (2H, m); 4.01 (1H, s); 4.07 (1H, s); 4.12–4.24 (4H, m); 7.28–7.34 (4H, m); 7.71–7.76 (4H, m).

IR (neat) 3497, 2971, 1741, 1594, 1452, 1341, 1159, 1093, 921, 814, 663 cm^{-1}.

(lit. ref. 95a, m.p. 88-100 °C).



239 **241** **242**

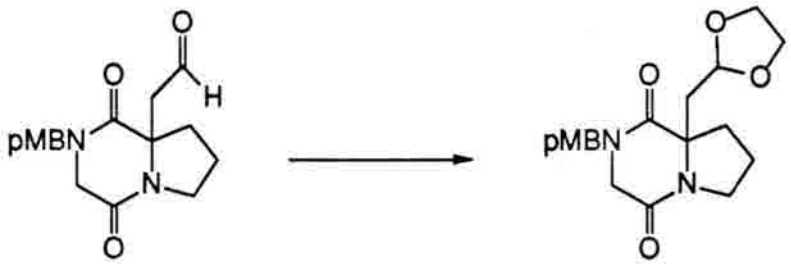
(±)-Ethyl 3(R*)-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-1-tol-uene-p-sulfonylpyrrolidine-2(S*)-carboxylate, (±)-Ethyl 3(S*)-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-1-tol-uene-p-sulfonylpyrrolidine -2(S*)-carboxylate (242)

To a stirred solution of **239** (360.2mg, 1.1mmol, 1.0eq) in pyridine (2.2mL) under Ar, at room temperature was added benzoyl chloride (0.51mL, 4.4mmol ,4.0eq) dropwise. The reaction mixture was stirred for two days, diluted with water, extracted with ethyl acetate, washed with 10% $CuSO_4$, brine, dried over $MgSO_4$, and concentrated to dryness. chromatography; radial, 1:3 ethyl acetate/hexane, yield; 222.8mg, 47%. (3:4 ratio of two diastereomers).

^1H NMR (300MHz) ($CDCl_3$) (diastereomer 1) δTMS 1.20 (3H, t, J = 7.2Hz); 1.57 (3H, s); 2.28 (1H, m); 2.43 (3H, s); 2.66 (1H, m); 3.45 (1H, m); 3.51 (1H, m); 4.14 (2H, m); 4.39 (1H, s); 7.48 (4H, m); 7.79 (2H, dd, J = 0.02, 0.005Hz); 7.90 (2H, dd, J = 0.02, 0.005Hz); 8.10 (1H, dd, J = 0.005, 0.02Hz).

IR (neat) 2986, 1725, 1600, 1453, 1349, 1278, 1158, 1093, 919, 815, 712, 663 cm^{-1}.

m.p. oil.



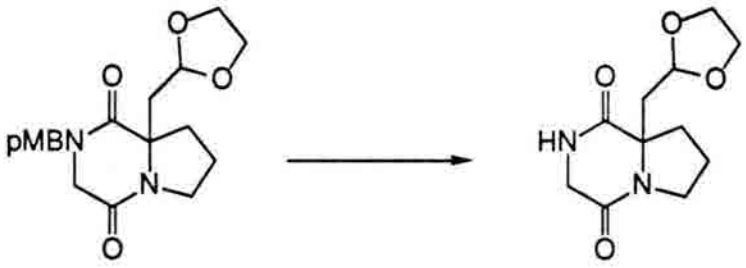
79 **256**

(±)-8a-[(1,3-Dioxolan-2-yl)methyl]-hexahydro-2-[(4-methoxyphenyl) methyl]-pyrrolo[1,2-a]pyrazine-1,4-dione (256)

To a stirred solution of **79** (396.4mg, 1.25mmol, 1.0eq) in a flask fitted with a dean-stark trap, in benzene (40 mL) was added ethylene glycol (0.077mg, 1.38mmol, 1.0eq) and toluenesulfonic acid (cat. amount). This solution was refluxed for 12 hours, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness to give a pale yellow amorphous solid. yield; 446.5mg, 99%.

^1H NMR (270 MHz) ($CDCl_3$) δTMS 1.99–2.34 (6H, m); 3.39–3.48 (1H, m); 3.64–3.73 (3H, m); 3.79 (3H, s); 3.84–3.91 (3H, m); 3.98 (1H, ½ ABq, J = 16.9Hz); 4.31 (1H, ½ ABq, J = 14.2Hz); 4.73 (1H, ½ ABq, J = 14.2Hz); 4.80 (1H, dd, J = 4.4, 5.5Hz); 6.86 (2H, d, J = 8.4Hz); 7.22 (2H, d, J = 8.4Hz).

IR (neat) 1661, 1514, 1449, 1173, 1032 cm^{-1}.



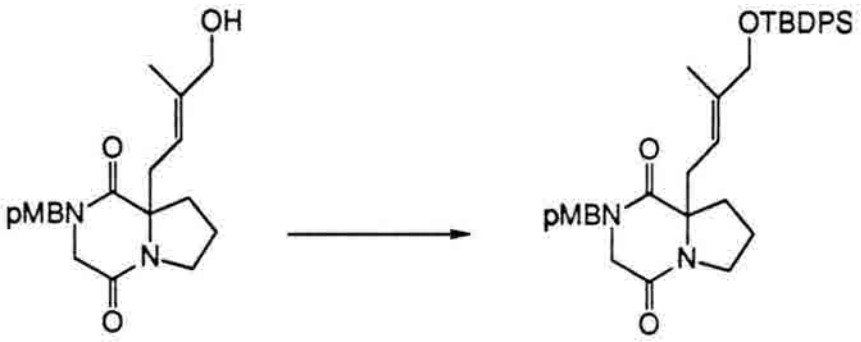
256 **257**

(±)-8a-[(1,3-Dioxolan-2-yl)methyl]-hexahydro-2*H*-pyrrolo[1,2-a] pyrazine-1,4-dione (257)

To a stirred solution of **256** (32.3mg, 0.0896mmol, 1.0eq) in water (0.34mL) and CH_3CN (0.67mL) was added CAN (186.7mg, 0.34mmol, 3.8eq). Two hours later the watery red solution was poured into a separatory funnel and extracted three times with $CHCl_3$ (20mL portions). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness to give a crude yield of 39mg. chromatography; PTLC, 89:9:1, CH_2Cl_2/methanol/NH_4OH (conc.). The product was obtained as an oily yellow solid. yield; 18.6mg, 86%

^1H NMR (270MHz) ($CDCl_3$) δTMS 1.99–2.28 (6H, m); 3.46–3.50 (1H, m); 3.83–3.95 (6H, m); 4.17 (1H, ½ABq, J = 16.8Hz); 4.92–4.94 (1H, br m); 6.50 (1H, br s, D_2O exch.)

IR (neat) 3249, 2885, 1661, 1455, 1326, 1126, 1044 cm^{-1}.



83 **261**

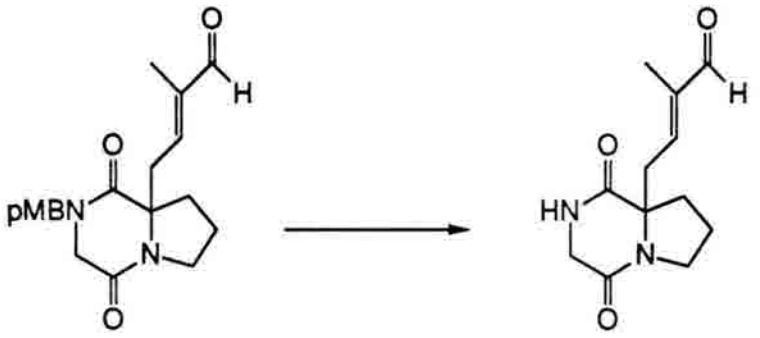
[±-(E)]-8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-hexahydro-2-[(4-methoxyphenyl)methyl]-pyrrolo[1,2-a]pyrazine-1,4-dione (261)

To a stirred solution of **83** (455.9mg, 1.272mmol, 1.0eq) in DMF (3.2mL) under N_2 was added imidazole (303mg, 4.45mmol, 3.5eq) followed by t-butyldiphenylchlorosilane (0.364mL, 1.40mmol, 1.1eq). After 15 hours, the resulting solution was diluted with water and extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. chromatography; radial, ethyl acetate, yield; 751.7mg, 99%.

^{1}H NMR (300MHz) ($CDCl_3$) δTMS 1.06 (9H, s); 1.52 (3H, s); 1.94–2.04 (2H, m); 2.17–2.25 (2H, m); 2.47 (1H, dd, J = 7.9, 14.0Hz); 2.62 (1H, dd, J = 7.9, 14.0Hz); 3.44–3.53 (1H, m); 3.66 (1H, ½ABq, J = 17.0Hz); 3.73 (3H, s); 3.76–3.87 (1H, m); 3.93 (1H, d, J = 3.6Hz); 3.98 (1H, ½ABq, J = 17.0Hz); 4.35 (1H, ½ABq, J = 14.3Hz); 4.55 (1H, ½ABq, J = 14.3Hz); 5.29–5.51 (1H, m); 6.79 (1H, dd, J = 2.0, 6.6Hz); 7.12 (1H, dd, J = 2.0, 6.6Hz); 7.36–7.46 (6H, m); 7.62–7.65 (4H, m).

IR (neat) 2932, 1661, 1514,1449, 1250, 1108, 703 cm^{-1}.

m.p. 105–106 °C, white crystalline solid.



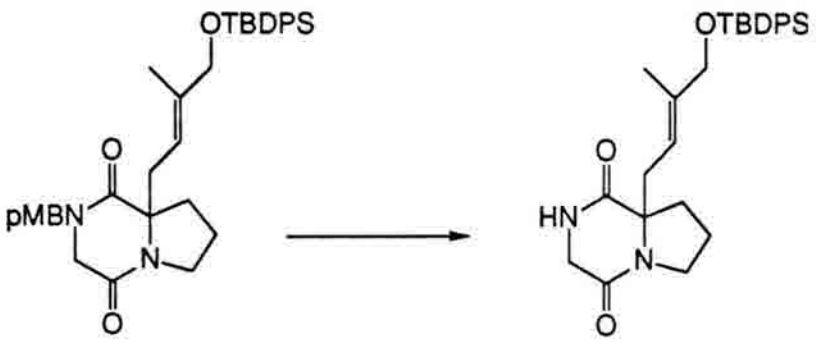
82 **260**

[±-(E)]-8a-[3-Methyl-2-buten-4-al]hexahydro-pyrrolo[1,2-a]pyrazine -1,4-dione (260)

To a stirred solution of **82** (14.8mg, 0.0135mmol, 1.0eq) in water (0.05mL) and acetonitrile (0.13mL) was added CAN (29.1mg, 0.0512mmol, 3.6mg). The solution was stirred for two hours, poured into a separatory funnel and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. chromatography; PTLC, 95:5:1 CH_2Cl_2/Methanol/acetic acid, (oil). yield; 3.2mg, quantitative.

^1H NMR (300MHz) ($CDCl_3$) δTMS 1.78 (3H, s); 2.00–2.28 (4H, m); 2.74 (1H, dd, J = 7.2, 14.8Hz); 2.89 (1H, dd, J = 8.2, 14.9Hz); 3.56–3.62 (1H, m); 3.82–3.96 (2H, m); 4.08 (1H, ½ABq, J = 17.2Hz); 6.47–6.52 (2H, m, 1H D_2O exch.); 9.45 (1H, s).IR (neat) 3261, 2920, 1655 (br), 1455 cm^{-1}.

m.p. oil.



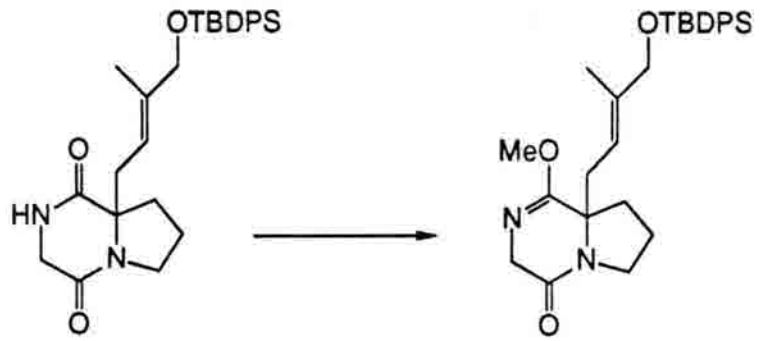
261 **262**

[±-(E)]-8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-hexahydro-2*H*-pyrrolo[1,2-a]pyrazine-1,4-dione (262)

To a stirred solution of **261** (120mg, 0.200mmol, 1.0eq) in CH_3CN (1.5mL) and water (0.77mL) was added CAN (417.4mg, 0.761mmol, 3.8eq). The orange solution was stirred one half hour, poured into a separatory funnel and extracted with chloroform. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. chromatography; radial, 95:5 ethyl acetate/methanol, (white crystalline solid). yield 41mg, 43%

^1H NMR (300MHz) ($CDCl_3$) δTMS 1.05 (9H, s); 1.57 (3H, s); 1.94–1.99 (2H, m); 2.01–2.21 (2H, m); 2.47–2.55 (1H, ddd, J = 8.5, 14.1, 28.8Hz); 2.57–2.64 (1H, dd, J = 7.6, 14.0Hz); 3.47–3.55 (1H, m); 3.74 (1H, d, ½ABq, J = 4.0, 16.8Hz); 3.80–3.87 (1H, m); 4.03 (2H, s); 4.10 (1H, ½ABq, J = 16.8Hz); 5.62 (1H, m); 6.03 (1H, d, J = 3.6Hz , D_2O exch.); 7.35–7.46 (6H, m); 7.62–7.65 (4H, m).

IR (neat) 3237, 2932, 1670, 1447, 1109, 701 cm^{-1}.



262 **263**

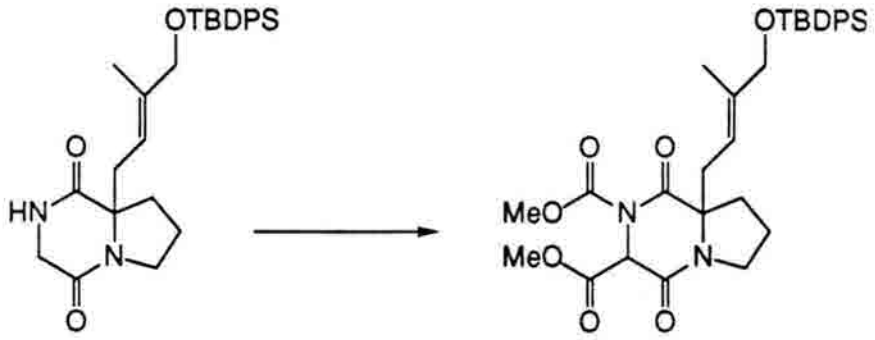
[±-(E)]-8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-tetrahydro-1-methoxy-pyrrolo[1,2-a]pyrazine-4-one (263)

A stirred solution of **262** (142.9mg, 0.09mmol, 1.0eq) in methylene chloride (1.0mL) under Ar was charged with Na_2CO_3 (37.8mg, 0.35mmol, 4.0eq). After 5 minutes Me_3OBF_4 (33.3mg, 0.0225mmol, 2.5eq) was added in one portion. Five and one half hours later saturated K_2CO_3 was added to the solution and stirred 5 minutes. The solution was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated. chromatography; PTLC, ethyl acetate, yield; 27.8mg, 63%.

^1H NMR (300MHz) ($CDCl_3$) δTMS 1.06 (9H, s); 1.53 (3H, s); 1.84–2.16 (4H, m); 2.43 (2H, d, J = 8.0Hz); 3.44–3.48 (1H, m); 3.71 (3H, s); 3.73–3.86 (1H, m); 4.00 (2H, s); 4.09 (2H, s); 5.47–5.53 (1H, m); 7.35–7.45 (6H, m); 7.63–7.66 (4H, m).

IR (neat) 2938, 2860, 1688, 1658, 1427, 1113 cm^{-1}.

m.p. oil.



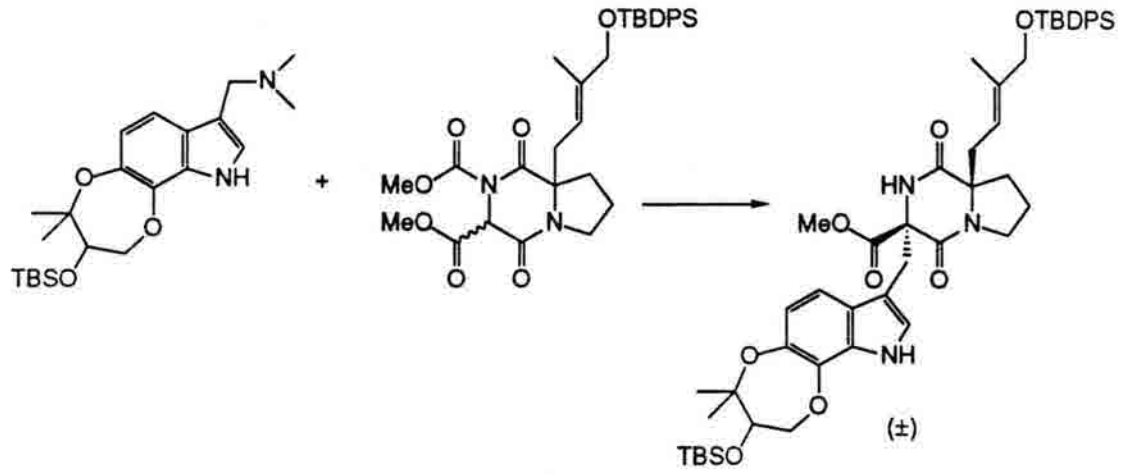
262 **265**

[(±)-[3α,8aβ,(E)]]-Methyl-8a-[4-[[(1,1-dimethylethyl)diphenyl-silyl]oxy]-3-methyl-2-butenyl]-octahydro-2-methoxycarbonyl-1,4-dioxo-pyrrolo[1,2-a]pyrazine-3-carboxylate (265)

To a stirred solution of **262** (99.1mg, 0.208mmol, 1.0eq) in THF (1.0mL) under Ar at –78 °C was added n-butyllithium (0.13mL, 0.208mmol, 1.0eq, 1.6M solution in hexanes) dropwise. The resulting solution was stirred for 0.5 hours when methylchloroformate (0.0177mL, 0.229mmol, 1.1eq) was added dropwise, and stirred 35 more minutes. At this time the solution was charged with an additional amount of methylchloroformate (0.0177mL, 0.229mmol, 1.1eq) and the resulting solution cannulated to a flask containing lithium bis-trimethylsilylamide (0.46mL, 0.457mmol, 2.2eq, 1.0M in THF) under Ar at –100 °C. This final solution was stirred for 1hour and 50 minutes, diluted with ethyl acetate, washed once with water, brine, ammonium chloride and back extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated. chromatography; radial, 1:1 hexane/ethyl acetate, (yellow oil). yield; 68.3mg, 55%.

^{1}H NMR (300MHz) ($CDCl_3$) δTMS 1.05 (9H, s); 1.56 (3H, s); 1.62–2.10 (2H, m); 2.20–2.31 (2H, m); 2.58 (2H, d, J = 8.0Hz); 3.44–3.52 (1H, m); 3.75–3.86 (1H, m); 3.85 (3H, s); 3.90 (3H, s); 4.04 (2H, d, J = 6.0Hz); 5.52 (2H, m); 7.36–7.42 (6H, m); 7.62–7.68 (4H, m).

IR (neat) 2955, 1790, 1737, 1678, 1432, 1273, 1220, 1108, 703 cm^{-1}.



220 **265** **266**

(±)-[3β,8aβ(E)]-methyl-3-[[3-[[1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxo-pyrrolo[1,2-a]pyrazine-3-carboxylate (266)

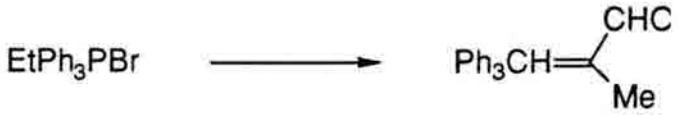
To a flask containing **265** (15.1mg, 0.255mmol, 1.0eq) and the gramine, **220** (1.3mg, 0.028mmol, 1.1eq) was added acetonitrile (0.5mL) and tributylphosphine (0.003mL, 0.0127mmol, 0.5eq). The resulting mixture was gently refluxed for three hours and stirred at room temperature overnight. The solution was diluted with ethyl acetate, washed with water, brine and dried over $MgSO_4$. The organic layer was evaporated leaving a crude oily solid. chromatography; PTLC; 1:2 ethyl acetate/hexane, (white crystalline solid). yield, 12.1mg, 53%.

^{1}H NMR (300MHz) ($CDCl_3$) δTMS (mixture of two racemic diastereomers) 0.14–0.15 (6H, m); 0.90 (18H, s); 1.04 (18H, s); 1.13 (6H, s); 1.46 (3H, s); 1.47 (3H, s); 1.56 (6H, s); 1.77–1.93 (4H, m); 2.05–2.17 (4H, m); 2.34 (2H, dd, J = 3.2, 11.6Hz); 2.45 (2H, dd, J = 7.4, 14.1Hz); 3.16 (1H, ½ ABq, J = 14.9Hz); 3.37 (1H, ½ ABq, J = 15.0Hz); 3.41–3.47 (2H, m); 3.64 (3H, s); 3.65 (3H, s); 3.71–3.97 (8H, m); 3.99 (4H, br s); 4.21 (2H, dd, J = 3.2, 11.6Hz); 5.44 (2H, m); 6.06 (1H, s, D_2O exch.); 6.08

(1H, s, D_2O exch.); 6.76 (1H, d, 8.5Hz); 6.96 (2H, br s); 7.07 (2H, d, J = 8.5Hz); 7.33–7.43 (12H, m); 7.64 (8H, dd, J = 1.6, 7.64Hz); 8.25 (2H, br s, D_2O exch.).

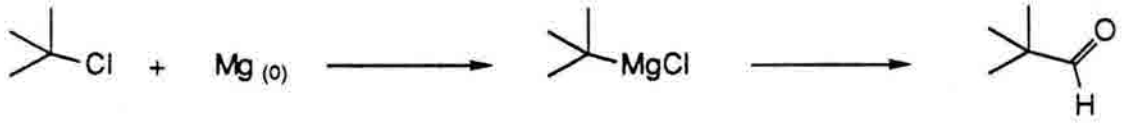
^{13}C NMR ($CDCl_3$) δ –4.83, –4.18, 13.57, 17.92, 19.16, 19.27, 19.48, 20.26, 25.72, 26.82, 28.03, 28.72, 29.62, 33.73, 33.95, 35.57, 46.05, 46.12, 53.35, 66.87, 68.02, 68.89, 71.65, 76.27, 80.67, 80.83, 108.15, 112.88, 117.06, 117.89, 117.95, 123.46, 123.55, 125.48, 127.64, 129.62, 133.65, 135.53, 136.74, 136.86, 138.84, 141.61, 141.79, 161.38, 169.66, 170.53, 170.61.

IR (neat) 3284, 2932, 1749, 1655, 1508, 1438, 1250, 1109, 703 cm^{-1}.



268

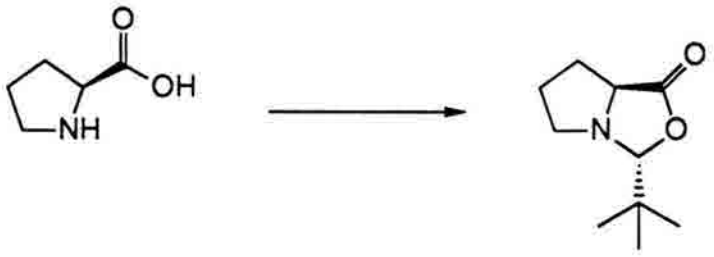
To a slurry of ethyl triphenylphosphoniumbromide (150g, 404mmol, 1.0eq) in THF (1225mL) at 0 °C under Ar was added n-BuLi (278mL, 445mmol, 1.1eq) via cannula. The resulting mixture was stirred for 0.5 hours and then a solution of potassium t-butoxide (50g, 445mmol, 1.1eq) in THF (318mL) was cannulated into the reaction flask. This mixture was stirred for another 30 min when ethyl formate (82mL, 1.01mol, 2.5eq) was added to the flask (via cannula). The mixture was stirred for 6 more hours, and then quenched by the addition of HCl (526mL, 1.0M). This was stirred 30 minutes and then 1M NaOH added until the pH ≈ 8–9. This was stirred a final 1.5 hours, and then the whole mixture extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. After concentration the crude product was recrystallized from CH_2Cl_2/diethyl ether, (white crystalline solid). yield; 90g, 70%.



267

A clean, three necked 5L flask fitted with a mechanical stirring rod, reflux condenser, and large addition funnel (1L). The entire apparatus was flame dried, flushed and kept under Ar. While the flask was still warm, newly ground magnesium turnings (215g,8.84mol, 1.05eq) and freshly distilled diethyl ether (2916mL) were added. The addition funnel was charged with t-butylchloride (916mL, 8.4mol, 1.oeq) and then it was slowly dribbled into the flask until the reaction was initiated (iodine was added to aid in this). Once the Grignard reaction had started the t-butylchloride was added slowly. After the addition the reaction mixture was refluxed for 30 minutes. The reaction mixture was allowed to settle for a number of hours. At this time the clear liquid was cannulated dropwise into a large, cold (–42 °C, dry ice/CH_3CN) flask charged with methyl formate (999mL, 16.2mol, 1.8eq). The reaction was stirred for an additional 30 minutes after the addition was complete. At this time the solution was poured onto a large quantity of ice and sulfuric acid. The whole mixture was taken up in ether. The organic layer was washed with brine, and dried over potassium chloride and stabilized with hydroquinone (4g). The ether was distilled off with a long helix packed column. The remaining oily solution was distilled with a similar fractionating column. The product was recovered at a temperature range of 69–72 °C. yield of pure pivaldehyde; 221g, 30.5%.

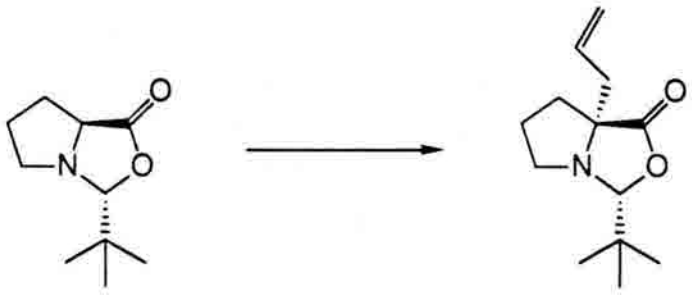
(lit. ref. 107, colorless oil).



(c) **86**

To a flask fitted with a dean stark trap was added finely powdered L-proline (109g, 947mmol, 1.0eq) pivaldehyde (408g, 4735mmol, 5.0eq) and pentane (3.5L). The mixture was slowly heated with vigorous stirring (stir motor) when a catalytic amount of TFA (1.6mL) was syringed into the flask. The mixture was refluxed for 10 days, until the required amount of water (aprox.18mL) was collected. The solution was carefully concentrated and the remaining residue subjected to the kugelrohr (100–105 °C) until no further distillate was observed. The purified product (colorless oil) was used immediately in the next step. yield; 156.2g, 93%.

(lit. ref. 38).

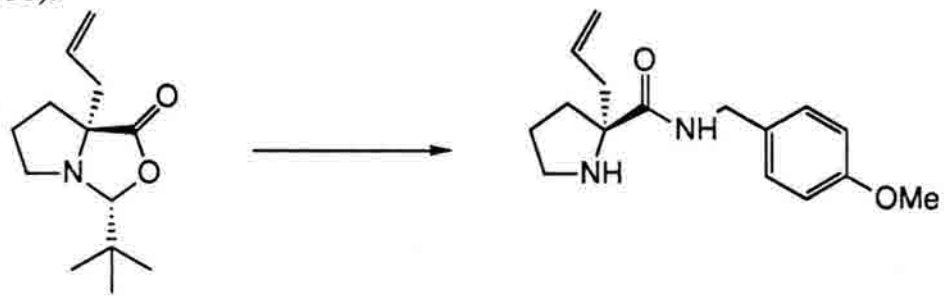


86 **87**

To a stirred solution of **86** (156g, 876mmol, 1,0eq) in THF (1.8L) under Ar, at –78 °C, was added a freshly prepared solution of LDA[n-BuLi (575mL,920mmol, 1.05eq,1.6M/hexanes) and $(Pr^i)_2NH$ (143mL, 920mmol, 1.05eq) in THF (1.0L) at 0 °C.] via cannula in 1 hour. The reaction mixture was stirred 1 hour more and then allyl bromide (83.3mL, 964mmol, 1,1eq) was added dropwise. After this addition the reaction mixture was stirred 1 hour 15min at –78 °C and 45min at r. t.. It was then poured into a large quantity of water and subsequently extracted with CH_2Cl_2. The organic layer was washed

with brine, dried over $MgSO_4$, concentrated and the yellowish oil subjected to kugelrohr distillation (100–110 °C, 6–7hours). The distillate was collected (colorless oil), and the tarry remainder discarded. yield; 160g, 82%. 76% for two steps

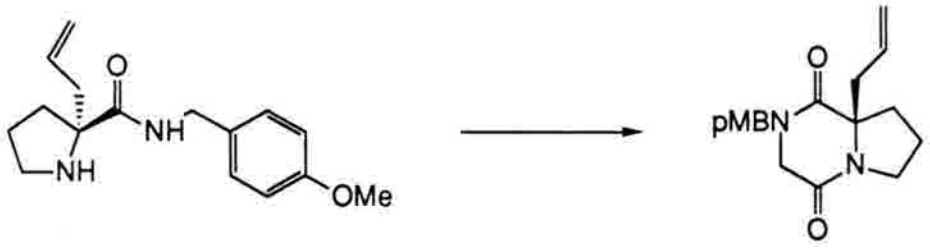
(lit. ref. 38).



87 **88**

To a flame dried 5L flask flushed with Ar and fitted with a rotary stirrer (motor attachment) was added 4-methoxybenzylamine (160mL, 1224mmol, 2.0eq) followed by distilled THF (960mL). The solution was cooled down to –78 °C and then n-BuLi (765mL, 1224mmol, 2.0eq, 1.6M/hexane) was added via cannula. After stirring 0.5 hours a cold (–78 °C) solution of **87** (133.5g, 612mmol, 1.0eq) in THF (480mL) was added via cannula. After 2 hours the cold bath was removed and the reaction stirred an additional hour. At this time the solution was concentrated until approx. 80% of the THF was removed. The remainder was poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The yellowish oil was subjected to kugelrohr distillation (85–98 °C) to remove the excess 4-methoxybenzylamine. yield; 167g, 99%.

(lit. ref. 24c,d).

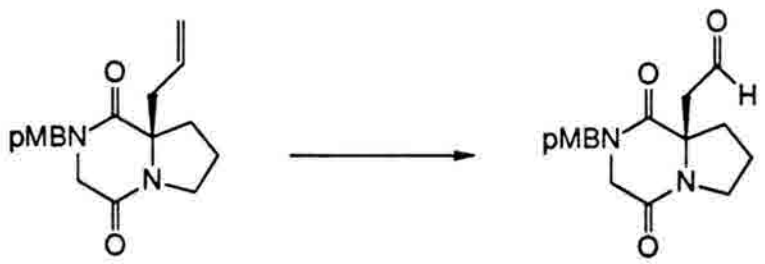


88 **89**

(R)-Hexahydro-2-[(4-methoxyphenyl)methyl]-8a-(2-propenyl)-pyrrolo[1,2-a]pyrazine-1,4-dione (89)

To a stirred solution of **88** (167g, 610mmol, 1.0eq) in CH_2Cl_2 (1968mL) was added a solution of K_2CO_3 (88.5g, 640mmol, 1.05eq, 0.5M/H_2O,1280mL) at 0 °C. After stirring vigorously for a time bromoacetyl bromide (58.4mL, 670mmol, 1.1eq) was added via cannula. The mixture was stirred approx. one hour when a 50% aqueous solution of NaOH (243mL, 122g) was added and the stirring continued overnight. The mixture was poured into water and the organic layer isolated, washed with dilute HCl, brine and dried over Na_2SO_4. The oily solid was recrystallized from CCl_4 to give 68g of the piperazinedione (white crystals). The remaining residue was subjected to chromatography; 2:1 hexane/ethyl acetate, 1:1 hexane/ethyl acetate, ethyl acetate, yield; 7.15g (partial separation). The remaining impure fractions were set aside. total recovered yield; 75g 39%.

(lit. ref. 24c,d).

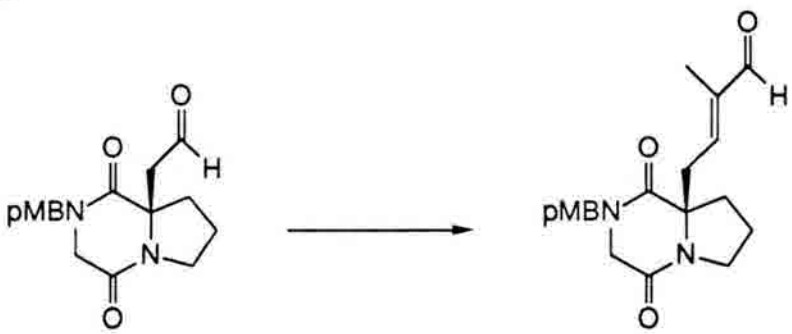


89 **90**

(R)-Hexahydro-2-[(4-methoxyphenyl)methyl]-1,4-dioxo-pyrrolo[1,2-a]pyrazine-8a(6H)-acetaldehyde (90)

A stirred solution of **89** (66.0g, 210mmol, 1.0eq) in methanol (1750mL) at –78 °C was subjected to ozone for 11 hours. At this time the reaction was quenched with dimethyl sulfide (42mL) and stirred for one hour at room temperature. The solvent was removed and the residue taken up in CH_2Cl_2. This was washed with water, brine and dried over $NaSO_4$. After concentrating, the crude product was chromatographed. chromatography; column, ethyl acetate, (oily solid). yield; 47g, 71%.

(lit. ref. 24c,d).



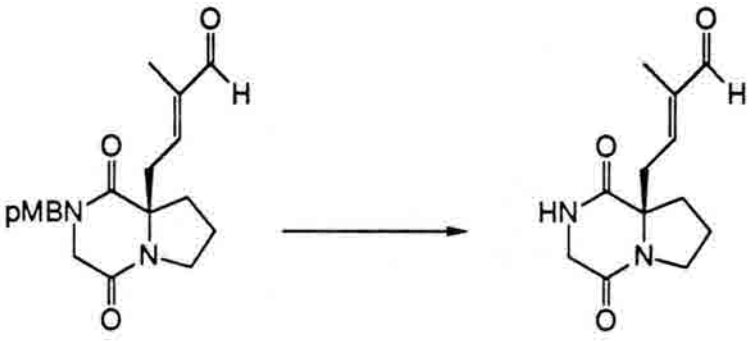
90 **91**

(R)-(E)-8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-hexahydro-2-[(4-methoxyphenyl)methyl]-pyrrolo[1,2-a]pyrazine-1,4-dione (91)

A stirred mixture of **90** (78.6g, 247.2mmol, 1.0eq) and $Ph_3P{=}(CH_3)CHO$ (82g, 260mmol, 1.05eq) in 1, 2-dichlorobenzene (687mL) was heated in an oil bath (65 °C) for 16 hours. The reaction solution was slowly cooled and the desired aldehyde crystallized

yielding 39.8g. The remaining solution was subjected to kugelrohr distillation to remove the dichlorobenzene. The crude product was recrystallized from methanol to give 19.2g. of a white solid. The remaining residue was set aside. total recovered yield; 59g, 67%. (lit. ref. 24c,d).

For all the pertinent spectral data for the last four reaction see Williams *et . al.* ref.24c.



91 **269**

(R)-(E)-8a-[3-Methyl-2-buten-4-al]hexahydro-pyrrolo[1,2-a]pyrazine -1,4-dione (269)

To a stirred solution of **91** (17.25g, 48.45mmol, 1.0eq) in a 2/1 solution of CH_3CN (343mL) and H_2O (171mL) was added in one portion, CAN (93g, 170mmol, 3.8eq). After 2 hours the orange solution was poured into a large separatory funnel and exhaustively extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. chromatography; column, 95:4:1, CH_2Cl_2/MeOH/AcOH, (yellow oil). yield; 9.0g, 79%. An analytical sample was obtained by PTLC, 1:1 hexane/ethyl acetate.

^1H NMR (300MHz) ($CDCl_3$) δ TMS 1.76 (3H, s); 1.99–2.10 (2H, br s); 2.17–2.26 (2H, m); 2.78 (1H, dd, J = 7.3, 14.5Hz); 2.90 (1H, dd, J = 8.0, 14.8Hz); 3.54–3.63 (1H, m); 3.84 (1H, dt, J = 12.3, 8.4Hz); 3.95 (1H, d½ABq, J = 3.4, 17.6Hz); 4.10 (1H, ½ABq, J = 17.6 Hz); 6.55 (1H, t, J = 7.2Hz); 7.96 (1H, br s, D_2O exch.); 9.45 (1H, s),

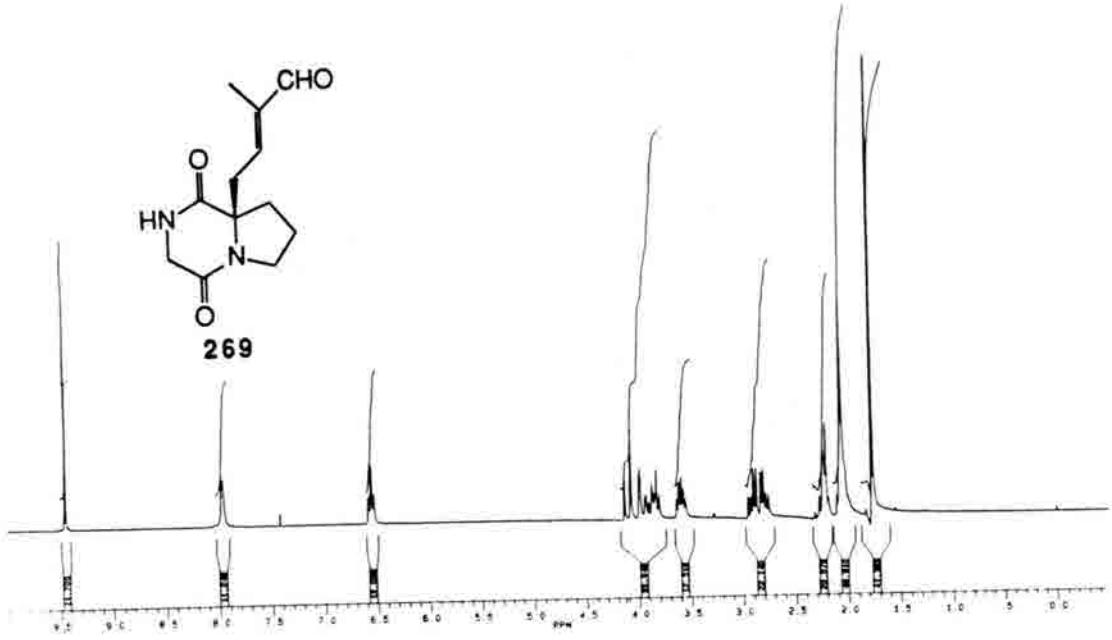
IR (neat) 3246, 1684, 1448, 1326, 1107 cm^{-1}.

$[\alpha]_{25}^{D} = -1.51/1.92x10^{-2} = -78.4$ (CH_2Cl_2, c = 0.164)

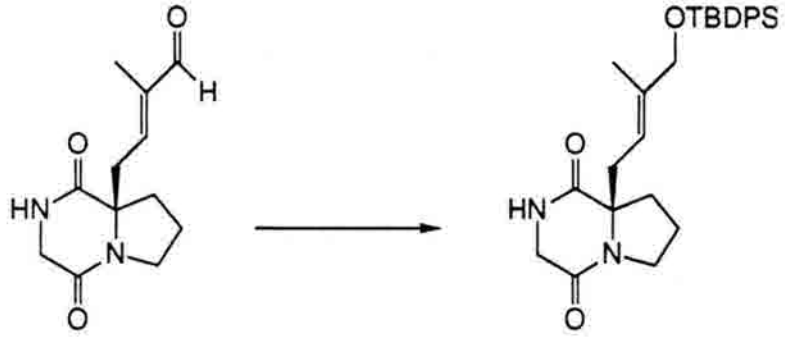
microanalysis calc'd. for: C, 61.00; H, 6.83; N, 11.86 found: C, 60.88; H, 6.66; N, 11.71.

EI HRMS 236.1155 ($C_{12}H_{15}N_2O_3$ requires 236.11609).

m.p. oil.



269



269 **270**

(R)-(E)-8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-hexahydro-2*H*-pyrrolo[1,2-a]pyrazine-1,4-dione (270)

To a stirred solution of **269** (9.0g, 37mmol, 1.0eq) in absolute ethanol (742mL) at room temperature, was added $NaBH_4$ (2.85g, 75.5mmol, 2.0eq). After 2 hours the excess

hydride was quenched with water (500mL) and the pH adjusted to 3–4 by the slow addition of 1M HCl. Fifteen minutes later, all the water and ethanol was removed and the crude reaction mixture was placed on the vacuum pump overnight. The resulting mass (10.87g) was triterated (1:4 CH_3OH/CH_2Cl_2) and filtered to remove the salts. The remaining solution was concentrated to yield 9.1g of the crude allylic alcohol, that was taken on immediately.

The crude allylic alcohol (9.1g, 38mmol, 1.0eq) was dissolved in DMF (191mL) stirred, and placed under Ar. To this flask was added imidazole (11.9g, 175.3mmol, 4.6eq) followed by t-BDPSCl (12.9mL, 49.5mL, 1.3eq). After 2 days the reaction mixture was diluted with water (1 liter) and extracted with a 1:1 solution of hexane and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The crude solid was recrystallized (ethyl acetate, two crops) to give 10.5g of the product. The remaining mother liquor was chromatographed (ethyl acetate) to give 3.0g of the pure product. yield; 13.5g, 75% from the enone (two steps). An analytical sample was recrystallized from acetone to provide a white crystalline solid.

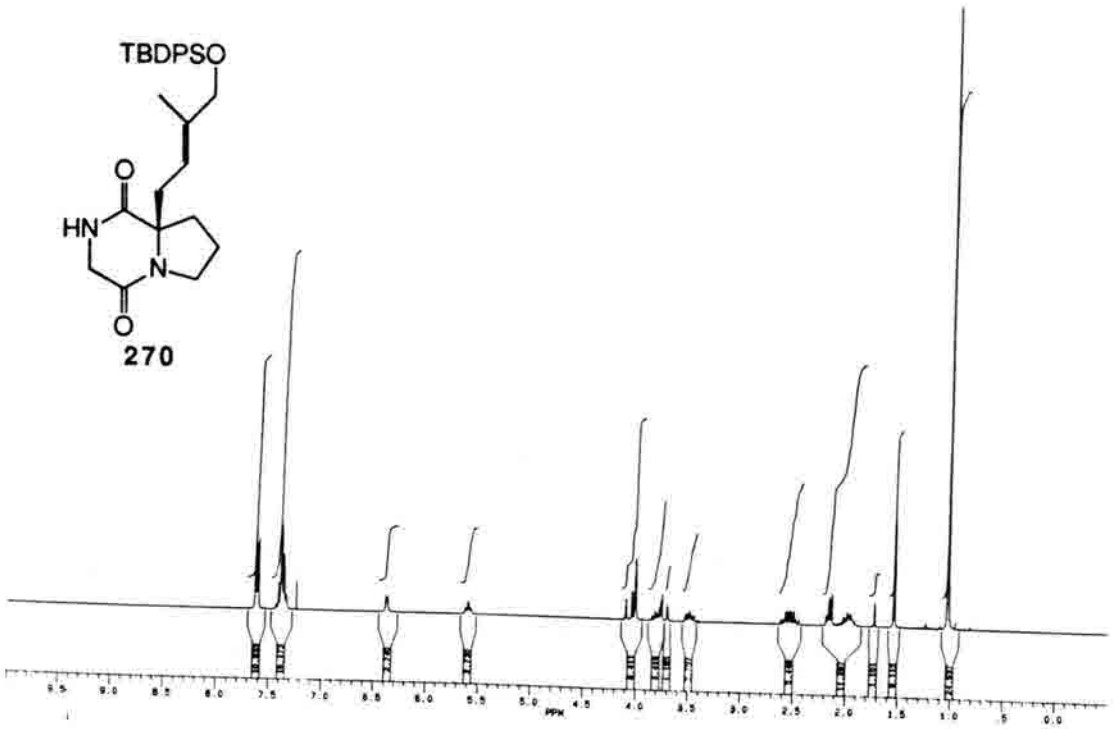
^1H NMR (300MHz) ($CDCl_3$) δ 1.03 (9H, s); 1.54 (3H, s); 1.92–2.19 (4H, m); 2.49 (1H, dd, J = 8.6, 14.1Hz); 2.58 (1H, dd, J = 7.5, 14.1Hz); 3.44–3.53 (1H, m); 3.73 (1H, d½ABq, J = 4.1, 16.9Hz); 3.78–3.85 (1H, m); 4.01 (2H, s); 4.06 (1H, ½ABq, J = 16.9Hz); 5.56–5.62 (1H, m); 6.38 (1H, d, J = 3.7Hz, D_2O exch.); 7.32–7.43 (6H, m); 7.62 (4H, dd, J = 1.8, 7.6Hz).

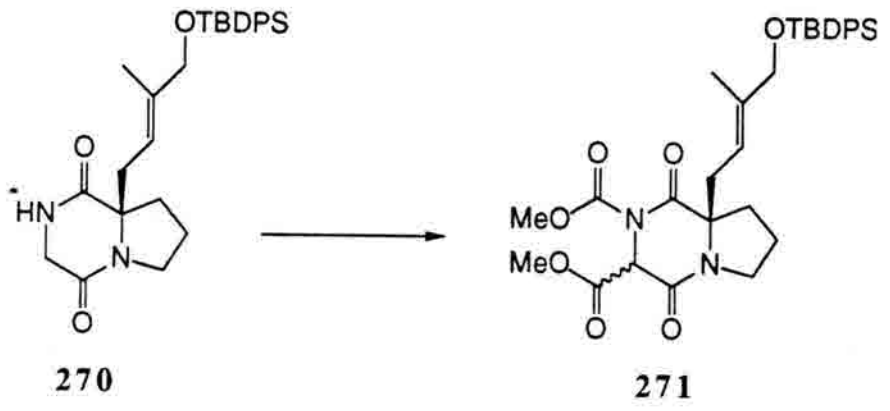
IR (neat) 3232 (br) 2930, 2857, 1664, 1446, 1435, 1113, 822, 733, 702 cm^{-1}.

$[\alpha]_{25}^{D} = -1.24/1.92x10^{-2} = -63.3$ ($CDCl_3$, c = 0.0822)

microanalysis cacl'd for $C_{28}H_{36}N_2O_3Si$: C,70.55; H, 7.61; N, 5.88 found C, 70.60; H, 7.56; N, 5.91.

m.p. 132 °C.





270 **271**

[(R)-[3αβ,8aβ,(E)]]-Methyl-8a-[4-[[(1,1-dimethylethyl)diphenyl-silyl]oxy]-3-methyl-2-butenyl]-octahydro-2-methoxycarbonyl-1,4-dioxo-pyrrolo[1,2-a]pyrazine-3-carboxylate (271)

To a stirred solution of **270** (8.12g, 17.0mmol, 1.0eq) in THF (208mL) at –78°C, was added a dropwise solution of n-BuLi (10.65mL, 17.03mmol, 1.0eq, 1.6M/hexane). After 25 minutes methyl chloroformate (1.45mL, 18.7mmol, 1.1eq) was syringed (dropwise) into the reaction flask, and stirred 25 more minutes. The solution was then

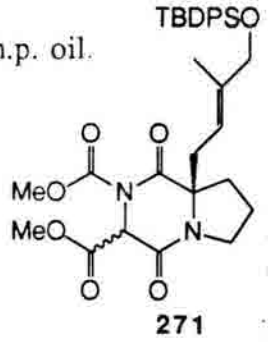
cannulated to a cold (–100 °C) flask charged with LiN $(SiCH_3)_2$ (37.47mL, 37.47mmol, 2.2eq, 1.0M/THF) and methyl chloroformate (1.45mL, 18.7mmol, 1.1eq). The resulting solution was stirred 45 additional minutes, diluted with ethyl acetate, washed with sat. NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and concentrated. chromatography; flash column, 2:1 hexane/ethyl acetate, yield; 9.4g, 93%. (mixture of two diastereomers, *anti/syn*; variable). An analytical sample was obtained by PTLC, 2:1 hexane/ethyl acetate.

^1H NMR (300MHz) ($CDCl_3$) δ 1.04 (9H, s); 1.40 (3H, s); 1.86–2.03 (2H, m); 2.12–2.31 (2H, m); 2.55 (1H, d, J = 7.4Hz); 3.43–3.52 (1H, m); 3.74–3.82 (1H, m); 3.83 (3H, s); 3.88 (3H, s); 4.03 (2H, br s); 5.48–5.53 (2H, m); 7.34–7.41 (6H, m); 7.57–7.66 (4H, m).

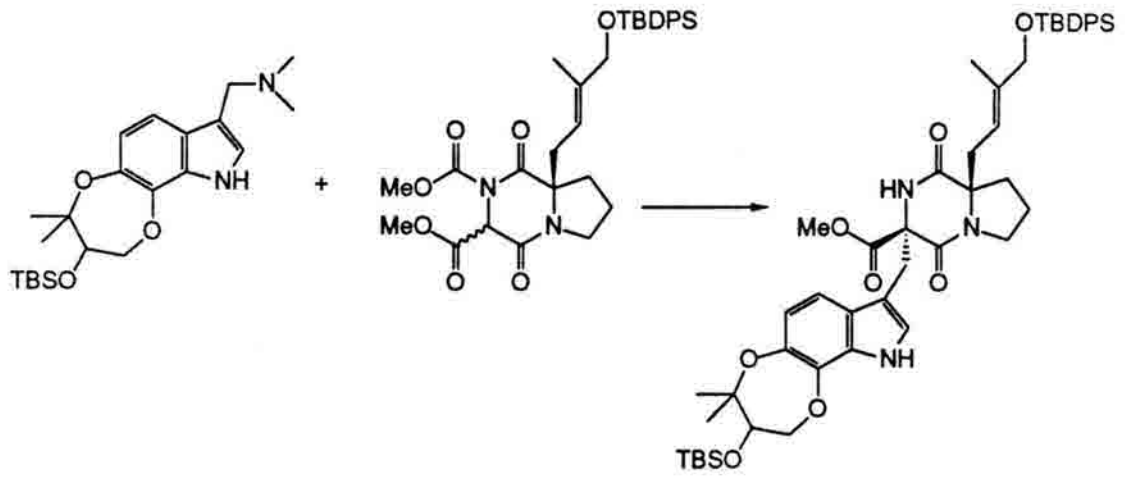
IR (neat) 2960, 1790, 1740, 1681, 1430, 1366, 1272, 1223, 1109, 735, 705 cm^{-1}.

microanalysis cacl'd for $C_{32}H_{40}N_2O_7Si$: C,68.06 H, 7.14; N, 4.96 found C, 67.87; H, 7.27; N, 4.77.

m.p. oil.



271



220 **271** **272**

[3β,8aβ(E)]-Methyl-3-[[3-[[1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxo-pyrrolo[1,2-a]pyrazine-3-carboxylate (272)

To a flask containing **271** (5.89g, 14.56mmol, 1.0eq) and **220** (8.64g, 14.56mmol, 1.1eq) was added CH_3CN (291mL) and tributylphosphine (1.82mL, 7.28mmol, 0.5eq). The resulting mixture was gently refluxed for 3.5 hours and then stirred at room temperature overnight. The solvent was removed and the crude product chromatographed. chromatography: column, 1:2 ethyl acetate/hexane, yield: 9.56g, 73%. An analytical sample was obtained by PTLC, 1:2 ethyl acetate/hexane, (white crystalline solid).

^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.10 (6H, s); 0.115 (3H, s); 0.12 (3H, s); 0.87 (9H, s); 0.88 (9H, s); 1.02 (18H, s); 1.096 (3H, s); 1.10 (3H, s); 1.45 (3H, s); 1.46 (3H, s); 1.54 (6H, s); 1.60–1.88 (6H, m); 2.02–2.11 (2H, m): 2.92 (2H, dd, J = 7.1, 14.4Hz); 2.44 (2H, dd, J = 8.1, 14.5Hz); 3.32–3.44 (4H, m); 3.60 (3H, s); 3.62 (3H, s); 3.72–3.93 (8H, m); 3.98 (4H, br s); 4.18 (2H, dd, J = 2.9, 8.4Hz); 5.43 (2H, m); 6.38 (1H, s, D_2O exch.); 6.41 (1H, s, D_2O exch.); 6.74 (1H, d, J = 8.5Hz); 6.75 (1H, d, J = 8.5Hz); 6.89 (1H, d, J = 2.3Hz); 6.92 (1H, d, J = 2.3Hz); 7.08

(2H, d, J = 8.5Hz); 7.33–7.41 (12H, m); 7.61–7.63 (8H, m); 8.43 (1H, d, J = 2.9Hz, D_2O exch.); 8.64 (1H, d, J = 1.9Hz, D_2O exch.).

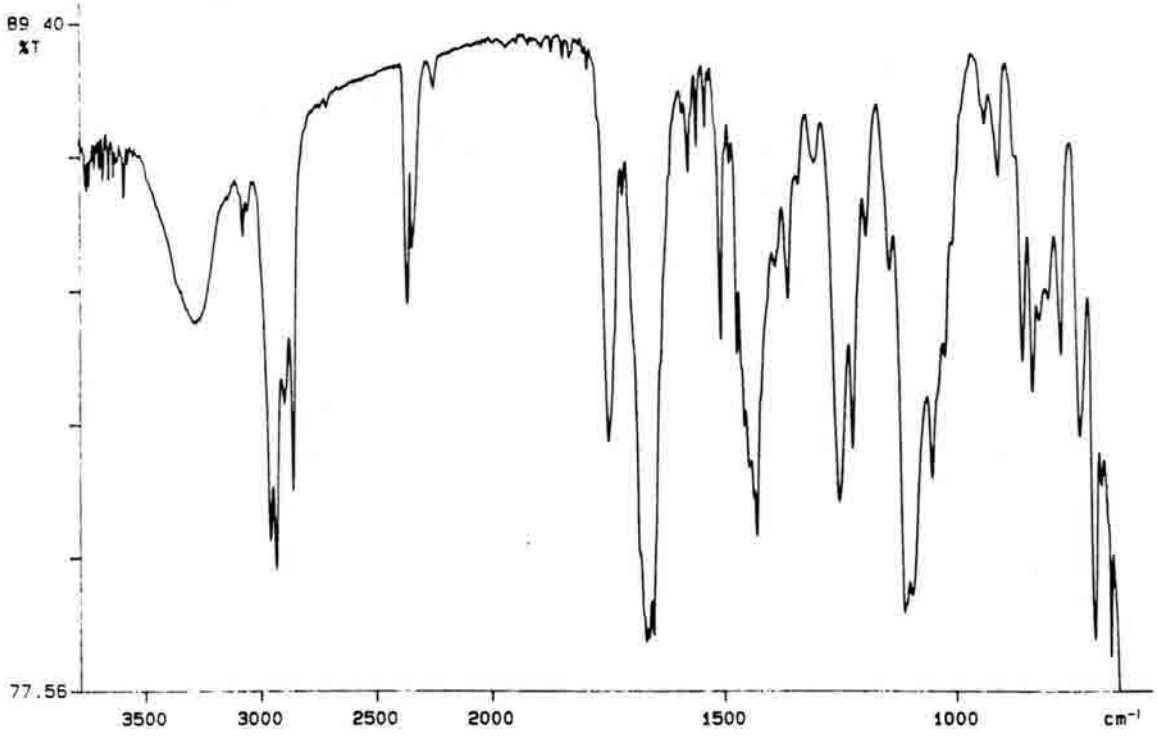
^{13}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 4.83, 4.19, 9.48, 17.92, 19.16, 19.27,19.48, 20.26, 25.72, 26.84, 28.03, 28.27, 29.69, 33.73, 35.57, 46.05, 46.19, 53.34, 66.87, 68.02, 71.65, 76.27, 80.67, 80.83, 108.15, 112.88, 117.06, 117.89, 117.95, 123.46, 123.55, 125.48, 127.64, 129.10, 129.18, 129.62, 133.64, 135.53, 138.84, 141.61, 141.78, 161.38, 169.66, 170.53, 170.60.

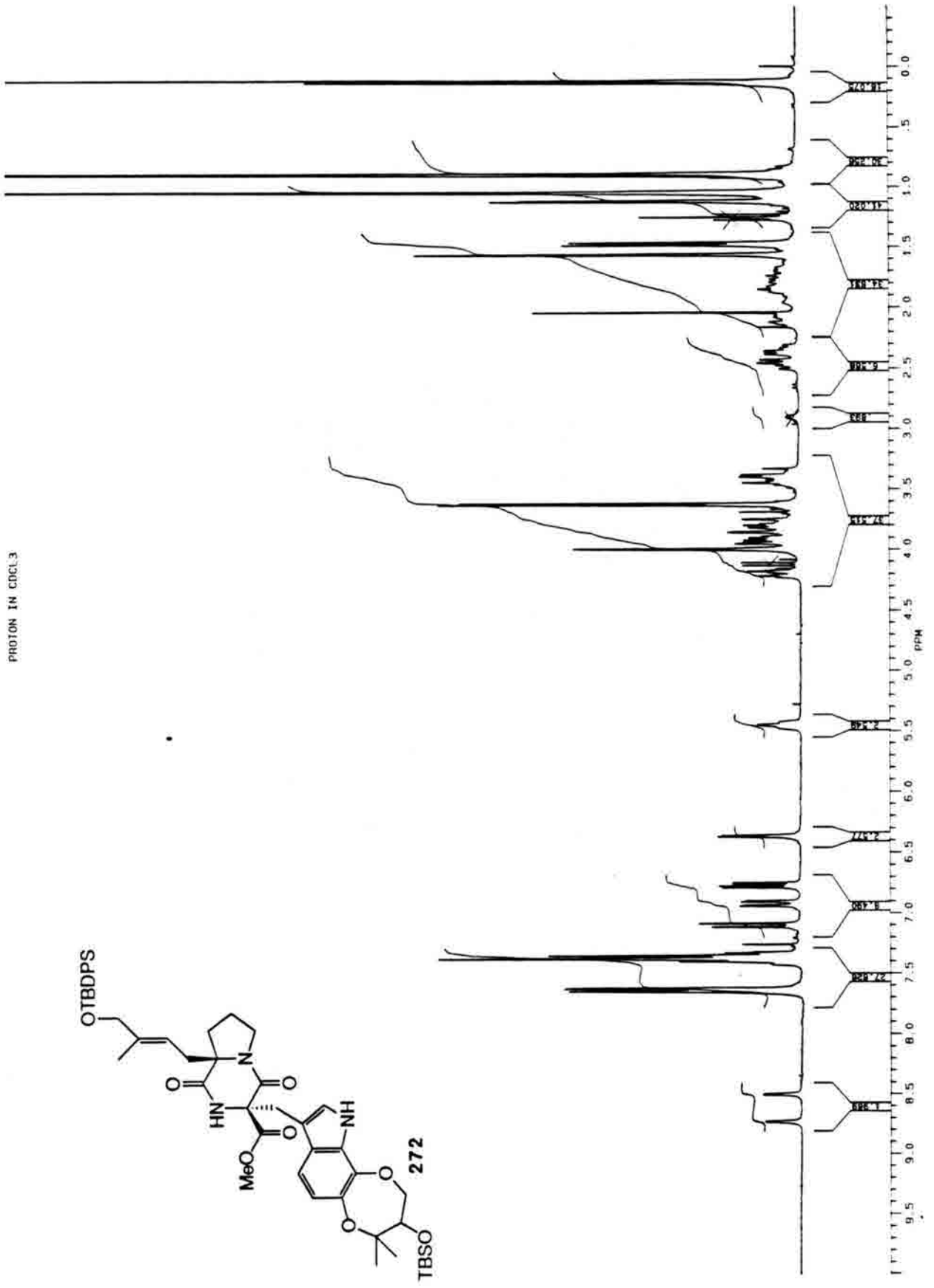
IR (neat) 3281 (br), 2954, 2932, 2856, 1747, 1670, 1665, 1649, 1431, 1251, 1224, 1109, 1088, 733, 706 cm^{-1}.

EI HRMS 893.4457 ($C_{50}H_{67}N_3O_8Si_2$ requires 893.4467).

microanalysis calc'd. for $C_{50}H_{67}N_3O_8Si_2$ C, 67.16; H, 7.55; N, 4.70; found C, 66.93; H, 7.36; N, 4.51.

m.p.106–108 °C.

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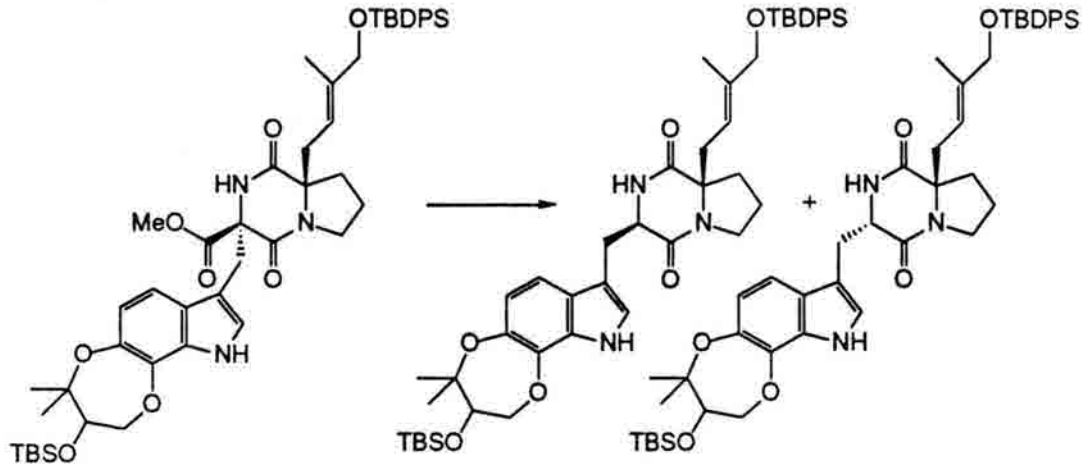
NH
TBSO
272
PPM



272 **273** **274**

[3β,8aβ(E)]8-[[8a-[[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole (273)

[3α,8aβ(E)]8-[[8a-[[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole (274

A flask containing **272** (9.56g, 10.7mmol, 1.0eq) and lithium chloride (2.26g, 53.45mmol, 5.0eq) under Ar was charged with HMPA (82mL) and water (0.29mL, 16.04mmol, 1.5eq). This mixture was gently heated (100 °C–105 °C) for 9 hours and then diluted with 1:1 hexane/ethyl acetate. The resulting solution was washed with water. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. chromatography; column, 1:2 ethyl acetate/hexane, yield; 2.10g, 23% (**274**, two di-astereomers, An analytical sample was obtained by PTLC, 1:2 ethyl acetate/hexane.) 5.90g, 66% (**273**, two diastereomers, An analytical sample was recrystallized from CCl_4.) total yield: 8.00g, 89%.

^{1}H NMR (300MHz) ($CDCl_3$) (**273**, mixture of two diastereomers) δTMS 0.146 (6H, s); 0.904 (18H, s); 1.04 (18H, s); 1.126 (3H, s); 1.13 (3H, s); 1.48 (6H, s); 1.64 (6H, s); 1.94–2.06 (6H, m); 2.20–2.24 (2H, m); 2.36–2.46 (2H, m); 2.60–2.72 (2H, m); 2.98 (2H, dd, J = 11.6, 14.1Hz); 3.44–3.57 (4H, m); 3.88 (2H, dd, J = 6.7,9.2Hz); 3.97 (2H, dd, J = 3.1, 9.1Hz); 4.02–4.06 (2H, m); 4.10 (4H, s); 4.17–4.25 (4H, m); 5.58 (2H, m); 5.68 (2H, br s, D_2O exch.); 6.75 (2H, d, J = 8.5Hz); 6.86 (1H, d, J = 2.2Hz): 6.88 (1H, J = 2.2Hz); 7.14 (2H, d, J = 8.4Hz); 7.26–7.44 (12H, m); 7.60–7.64 (8H, m); 8.04 (1H, s, D_2O exch.); 8.06 (1H, s, D_2O exch.).

syn-diastereomers separated;

^{1}H NMR (300MHz) ($CDCl_3$) (**273a**, less polar) δTMS 0.12 (3H, s); 0.13 (3H, s); 0.88 (9H, s); 1.03 (9H, s); 1.11 (3H, s); 1.46 (3H, s); 1.63 (3H, s); 1.92–2.04 (3H, m); 2.18–2.23 (1H, m); 2.39 (1H, dd, J = 7.2, 14.2Hz); 2.64 (1H, dd, J = 8.7, 14.2Hz); 2.99 (1H, dd, J = 11.4, 14.2Hz); 3.42–3.46 (1H, m); 3.51 (1H, dd, J = 2.7, 14.2Hz); 3.85 (1H, dd, J = 9.2, 11.3Hz); 3.94 (1H, dd, J = 3.0, 9.Hz); 3.99–4.06 (1H, m); 4.08 (2H, s); 4.11–4.15 (1H, m); 4.19 (1H, dd, J = 3.0, 11.3Hz); 5.58 (1H, t, J = 7.8Hz); 5.76 (1H, d, J = 2.7Hz, D_2O exch.); 6.73 (1H, d, J = 8.4Hz); 6.85 (1H, d, J = 2.1Hz); 7.11 (1H, d, J = 8.5Hz); 7.26–7.42 (6H, m); 7.57–7.63 (4H, m); 8.15 (1H, s, D_2O exch.).

^{1}H NMR (300MHz) ($CDCl_3$) (**273b**, more polar) δTMS 0.12 (3H, s); 0.14 (3H, s); 0.88 (9H, s); 1.03 (9H, s); 1.11 (3H, s); 1.46 (3H, s); 1.62 (3H, s); 1.91–2.04 (3H, m); 2.18–2.22 (1H, m); 2.36 (1H, dd, J = 7.3, 14.2Hz); 2.60 (1H, dd, J = 8.6, 14.3Hz); 2.97 (1H, dd, J = 11.3, 14.2Hz); 3.41–3.44 (1H, m); 3.50 (1H, dd, J = 3.1, 14.2Hz); 3.86 (1H, dd, J = 9.3, 11.3Hz); 3.95 (1H, dd, J = 3.0, 9.1Hz); 3.99–4.03 (1H, m); 4.08 (2H, s); 4.14–4.16 (1H, m); 4.20 (1H, dd, J = 2.9, 11.6Hz); 5.56 (1H, t, J =7.5Hz); 5.72 (1H, d, J = 2.6Hz, D_2O exch.); 6.73 (1H, d, J = 8.4Hz); 6.84 (1H, d, J = 2.1Hz); 7.11 (1H, d, J = 8.4Hz); 7.26–7.42 (6H, m); 7.57–7.62 (4H, m); 8.07 (1H, s, D_2O exch.).

^{1}H NMR (300MHz) ($CDCl_3$) (**274**, mixture of two diastereomers) δTMS 0.14 (6H, s); 0.16 (6H, s); 0.90 (18H, s); 1.04 (9H, s); 1.045 (9H, s); 1.09 (3H, s); 1.13 (3H, s); 1.47 (6H, s); 1.53 (3H, m); 1.54 (3H, m); 1.97–2.17 (8H, m); 2.47–2.62 (4H, m); 2.78–2.88 (2H, m); 3.54–3.65 (4H, m); 3.82–3.99 (6H,m); 4.02 (4H, s); 4.21 (2H, dd, J = 3.1, 11.0Hz); 4.35–4.39 (2H, m); 5.52–5.54 (2H, m); 5.69 (2H, br s, D_2O exch.); 6.60 (1H, d, J = 8.4Hz); 6.63 (1H, d, J = 8.4Hz): 6.89 (2H, d, J = 2.1Hz); 6.98 (2H, d, J = 8.4Hz); 7.36–7.42 (12H, m); 7.62–7.69 (4H, m); 8.08 (2H, br s, D_2O exch.).

IR (neat) *(anti)* 3289 (br), 2929, 2855, 1666, 1444, 1428, 1254, 1222, 1111, 857, 836, 704 cm^{-1}.

IR (neat) *(syn)* 3274 (br), 2929, 2858, 1666, 1651, 1453, 1428, 1250, 1224, 1112, 1052, 858, 838, 777 cm^{-1}.

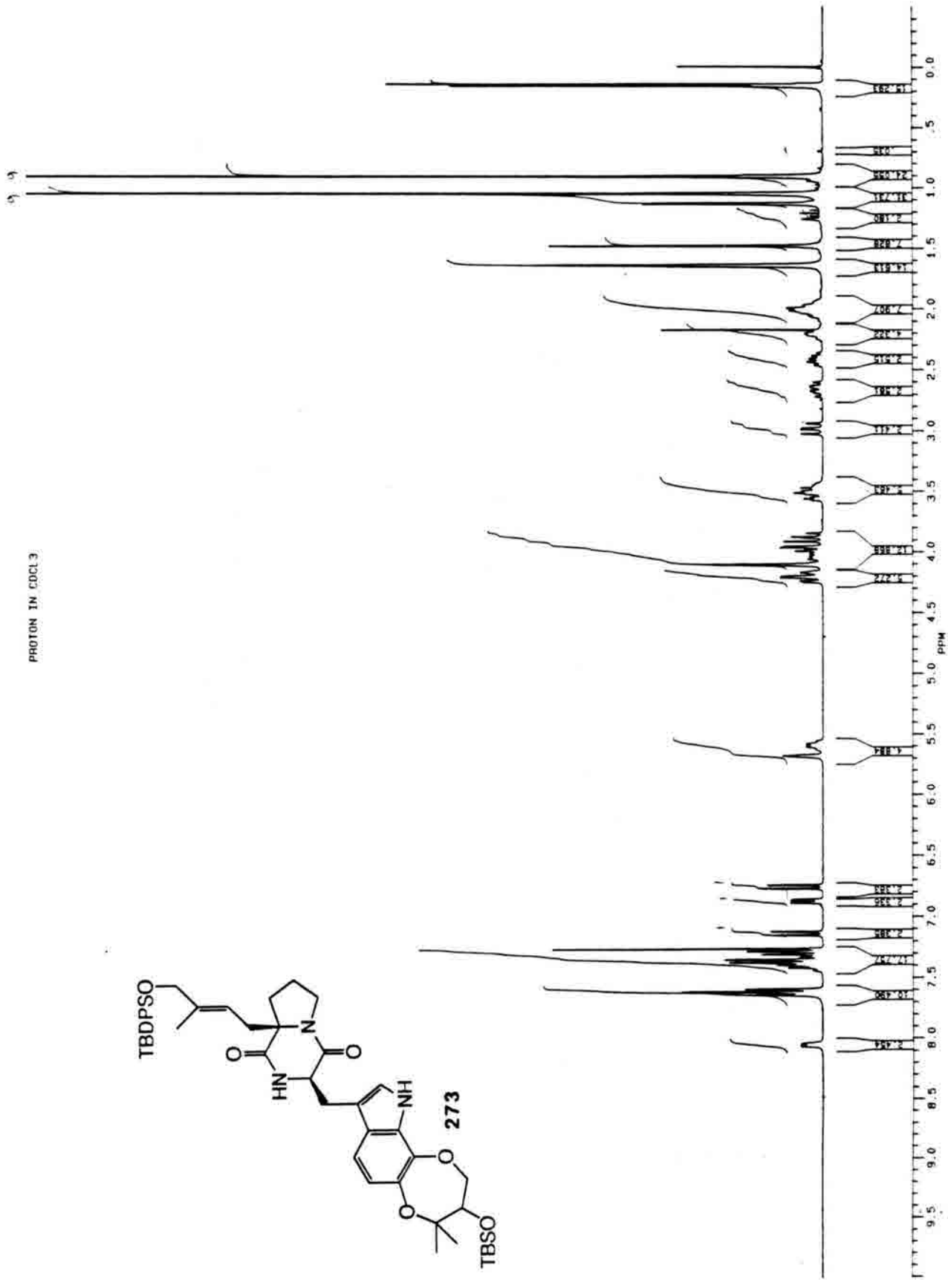
microanalysis cacl'd. for $C_{49}H_{65}N_3O_6Si_2$ *(syn)*: C, 68.94; H, 7.84; N, 5.02 Found: C, 69.06; H, 7.76; N, 5.03.

m.p. *(syn)* 167–168°C, white foamy solid.

MS (EI) *(anti)* 833 *m/e* (rel intensity) 833 (M^+, 0.1) 512 (6.4) 361 (26) 360 (100) 199 (47).

microanalysis cacl'd for $C_{48}H_{65}N_3O_6Si_2$ *(anti)*: C, 68.94; H, 7.84; N, 5.02 Found: C, 68.76; H, 7.60; N, 4.82.

m.p. *(anti)* 95–99 °C, white crystalline solid.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HN
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O
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O
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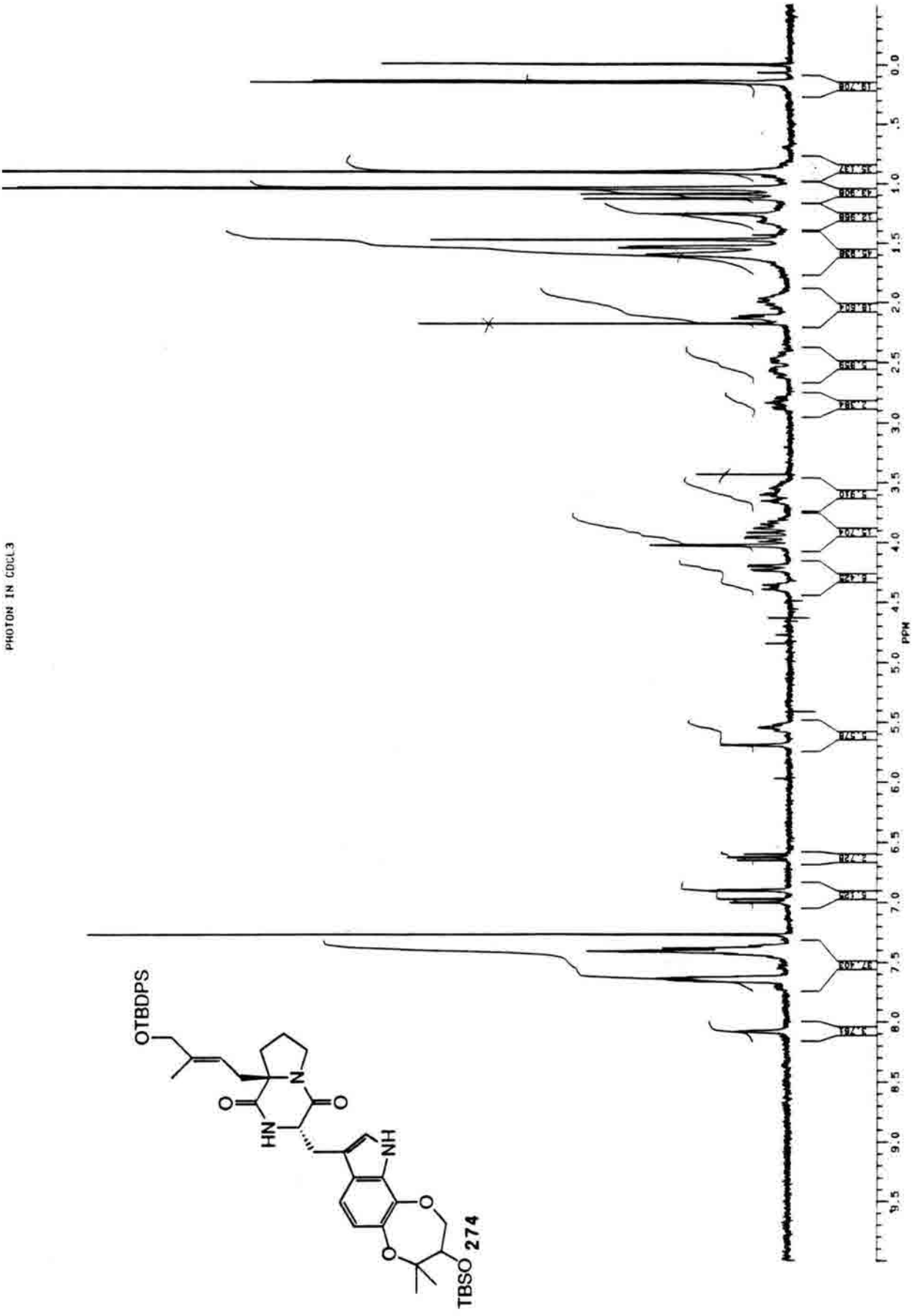
O
TBSO
273


PHOTON IN CDCL3
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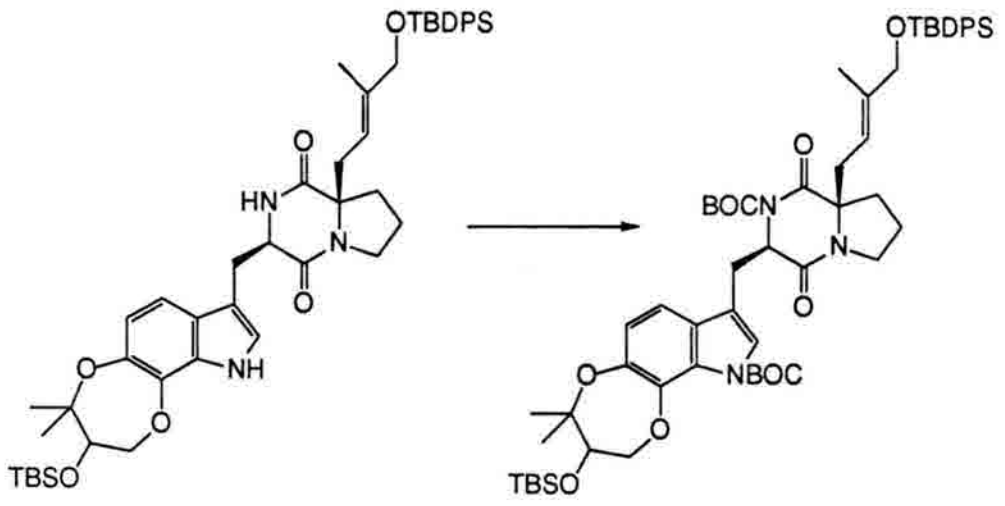
PPM



273 **278**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[2-[(1,1-dimethylethoxy)carbonyl]-8a-[4-[[1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethyl-silyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (278)

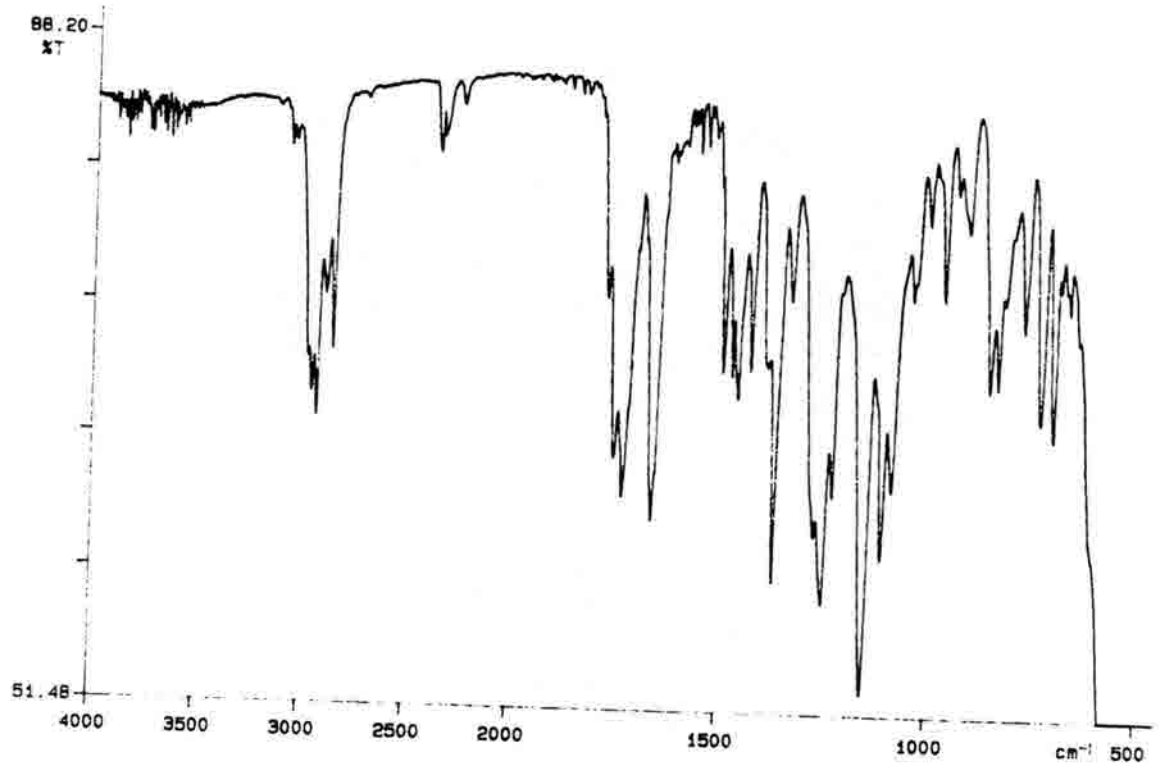
To a stirred solution of **273** (310mg, 0.371mmol, 1.0eq) at 0°C under Ar in CH_2Cl_2 (7.4mL) was added Et_3N (0.104mL, 0.743mmol, 2.0eq) and DMAP (90.7mg, 0.743mmol, 2.0eq). After 5 minutes, $(BOC)_2O$ (486.2mg, 2.23mmol, 6.0eq) was added in one portion. The resulting solution was stirred 8.5 hours, poured into water and extracted with ethyl acetate. The organic layer was washed with 10% $CuSO_4$, brine, dried over $MgSO_4$ and concentrated. chromatography; radial, 1:2 ethyl acetate/hexane. The product was obtained as a foamy solid. yield; 375mg, 97%.

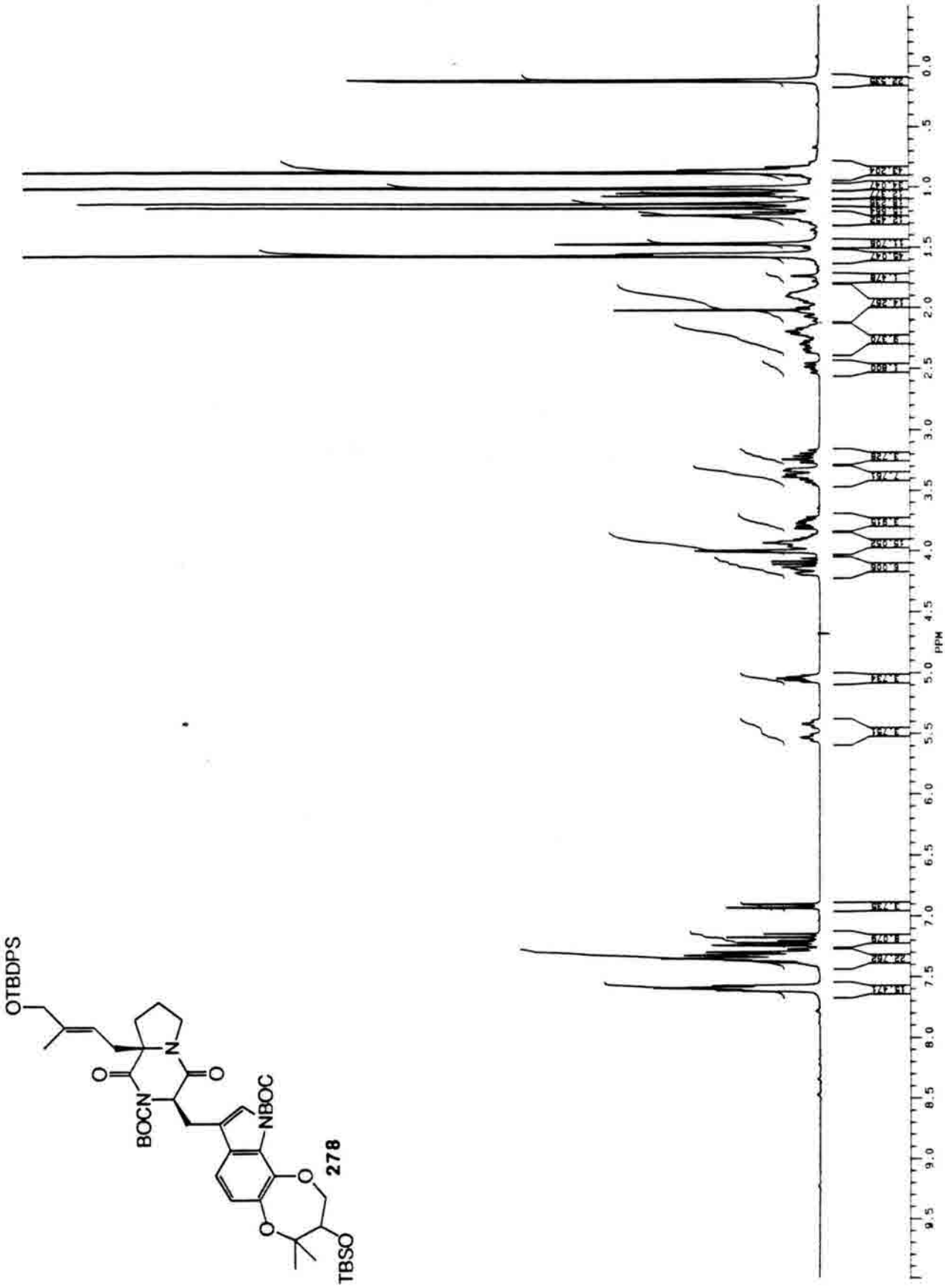
^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.12 (6H, s); 0.13 (6H, s); 0.879 (9H, s); 0.880 (9H, s); 1.01 (18H, s); 1.05 (3H, s); 1.07 (3H, s); 1.14 (9H, s); 1.18 (9H, s); 1.55 (6H, s); 1.47 (6H, s); 1.57 (18H, s); 1.88–2.16 (6H, m); 2.17–2.26 (2H, m); 2.28–2.36 (2H, m); 2.50 (2H, dd, J = 8.1, 14.5Hz); 3.22 (2H, m); 3.32–3.45 (4H, m); 3.71–3.81 (2H, m); 3.84–3.96 (4H, m); 4.00 (4H, br s); 4.13–4.18 (2H, m); 5.02–5.07 (2H, m); 5.42 (1H, t, J = 7.3Hz); 5.53 (1H, t, J = 7.5Hz); 6.91 (2H, d, J =

8.3Hz); 7.16 (1H, d, J = 8.0Hz); 7.19 (1H, d, J = 8.2Hz);7.22 (1H, s); 7.24 (1H, s); 7.30–7.40 (12H, m); 7.57–7.61 (8H, m).

IR (neat) 2932, 1752, 1730, 1660, 1371, 1251, 1153, 1109, 1088, 706 cm^{-1}.

EI HRMS 1035.5481 ($C_{58}H_{81}N_3O_{10}Si_2$ requires 1035.5461).

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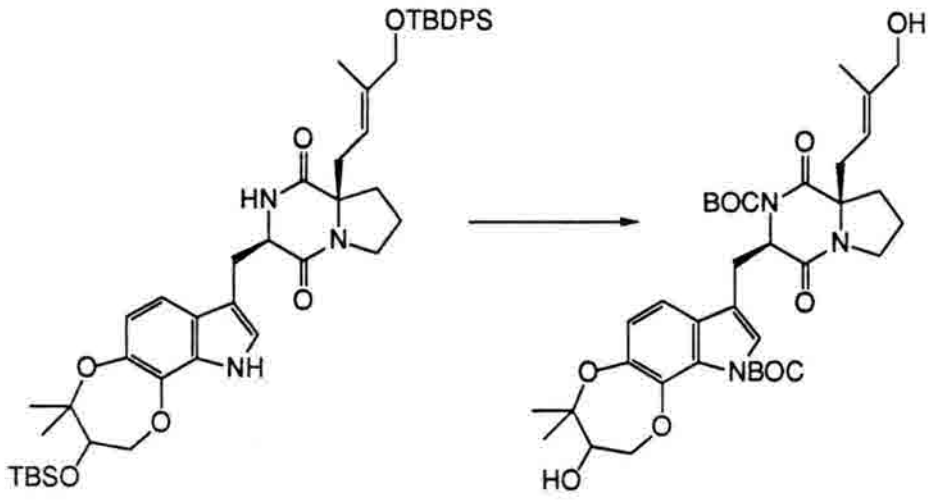
278
TBSO
PPM



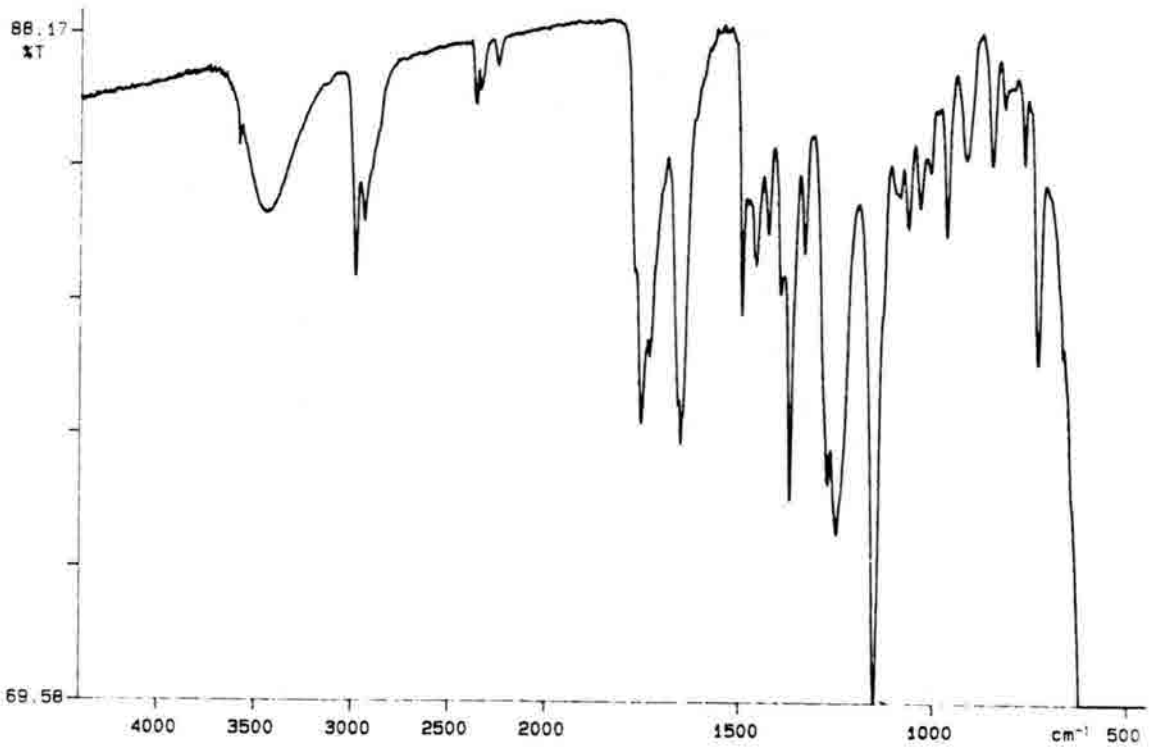
273 **279**

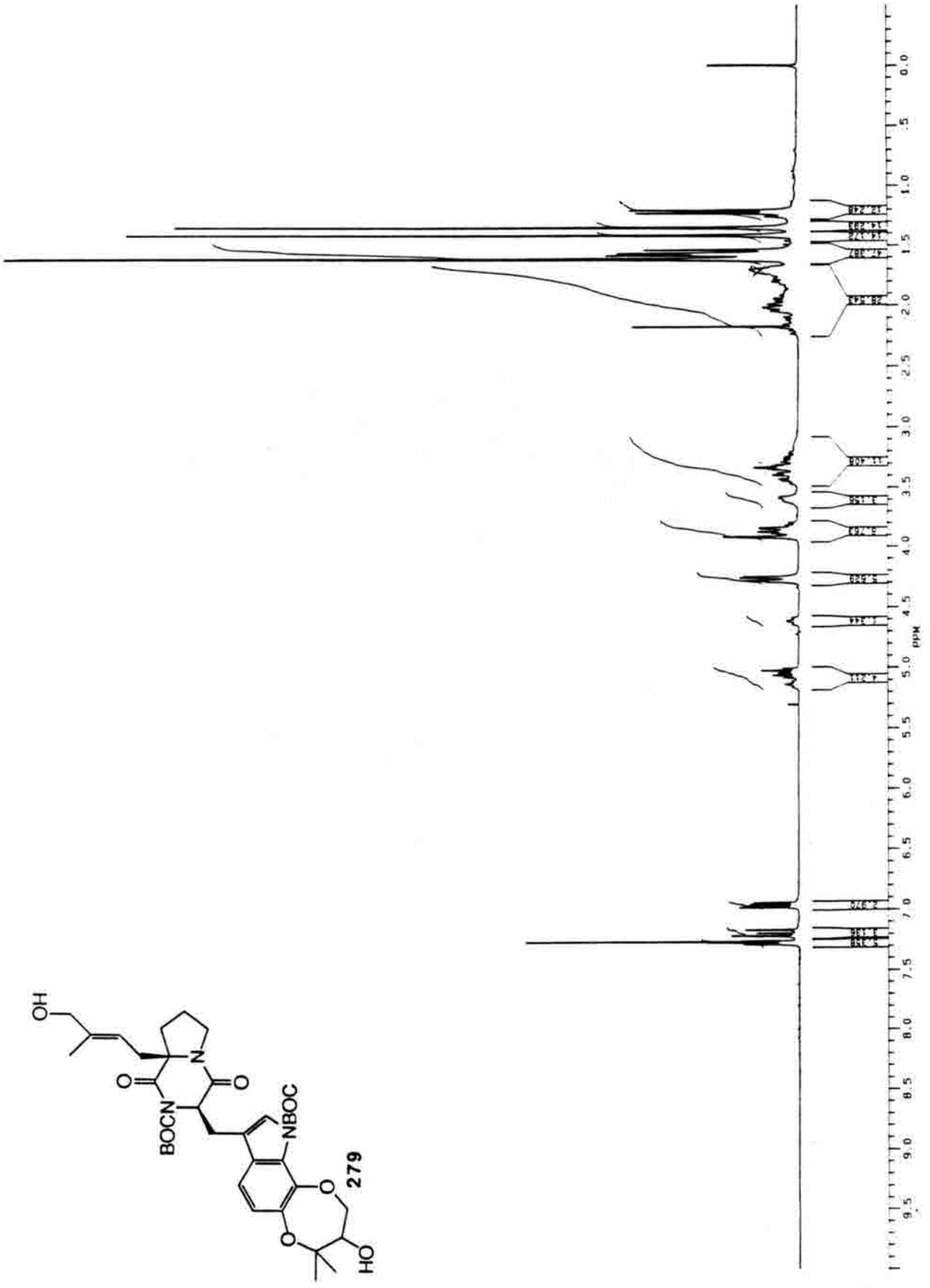
[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[2-[(1,1-dimethylethoxy)carbonyl]-8a-[4-hydroxy-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-4,4-dimethyl-3-hydroxy-2H,10H-[1,4]dioxepino-[2,3g]indole-10-carboxylate (279)

To a stirred solution of **278** (511mg, 0.612mmol, 1.0eq) at 0 °C under Ar in CH_2Cl_2 (12.2mL) was added DMAP (149.4mg, 0.1.22mmol, 2.0eq) and Et_3N (0.170mL, 1.22mmol, 2.0eq). After 5 minutes, $(BOC)_2O$ (801.0mg, 3.67mmol, 6.0eq) was added in one portion. The resulting solution was stirred 2.7 hours, and found to be complete by TLC, during this period the ice in the bath melted reaching a temperature of 15 °C. The reaction flask was then charged with THF (12mL) and the CH_2Cl_2 removed by evaporation (until the volume of the flask was approx. 12mL). The solution was stirred at room temperature and n-Bu_4NF (1.96mL, 1.96mmol, 3.2eq, 1.0M/THF) added quickly. After 22 hours, an additional amount of n-Bu_4NF (1.0mL, 1.0mmol, 1.6eq, 1.0M/THF) was added to the reaction flask and stirred one more day. The reaction was complete by TLC, so it was poured into water and extracted with ethyl acetate. The organic layer was washed with 10% $CuSO_4$, brine, dried, over $MgSO_4$ and concentrated. chromatography; radial, ethyl acetate. The product was obtained as a pale yellow foamy solid. yield; 369mg, 89%.

^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.21 (3H, s); 1.24 (3H, s); 1.29 ((9H, s); 1.35 (9H, s); 1.47 (6H, s); 1.52 (6H, s); 1.56 (18H, s); 1.63–2.21 (14H, m); 3.21–3.38 (8H, m); 3.54 (1H, br s, D_2O exch.); 3.58 (1H, br s, D_2O exch.); 3.81–3.87 (6H, m, 2H D_2O exch.); 4.22 (4H, d, J = 8.0Hz); 4.62 (1H, t, J = 8.4Hz); 4.96–5.01 (2H, m); 5.07 (1H, t, J = 7.2Hz); 6.90 (1H, d, J = 8.4Hz); 6.91 (1H, d, J = 8.4Hz); 7.13 (1H, d, J = 8.4Hz); 7.18 (1H, d, J = 8.4Hz); 7.22 (1H, s); 7.23 (1H, s).

IR (neat) 3436, 2978, 1755, 1649, 1367, 1249, 1149, 732 cm^{-1}.

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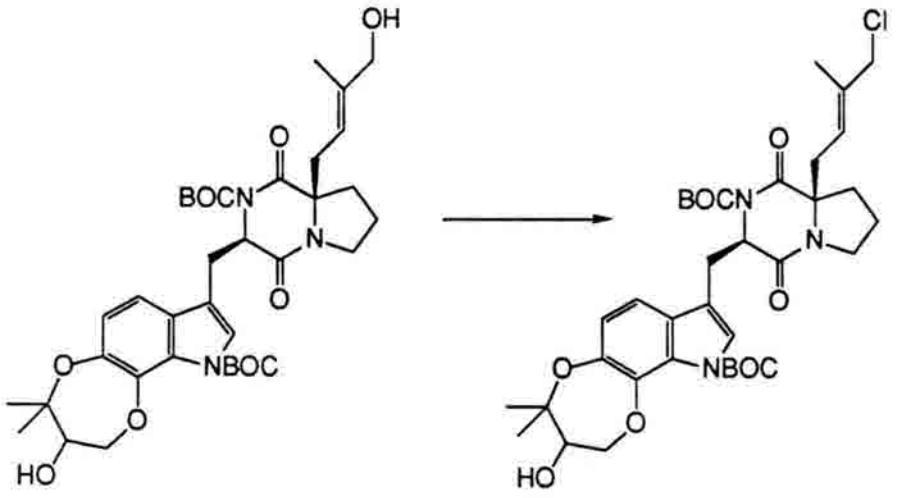
NBOC
O
O
O
HO
279
ppm



279 **280**

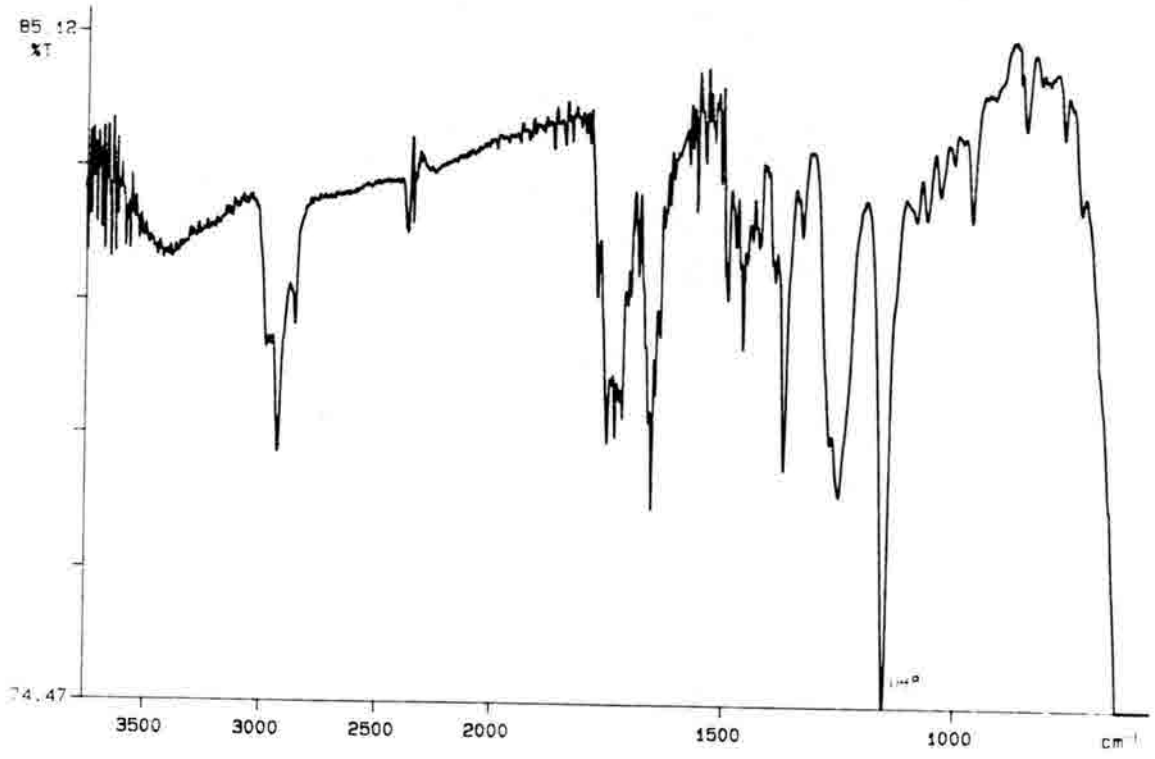
[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[2-[(1,1-dimethylethoxy)carbonyl]-8a-[4-chloro-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-4,4-dimethyl-3-hydroxy-2H,10H-[1,4]dioxepino-[2,3-g]indole-10-carboxylate (280)

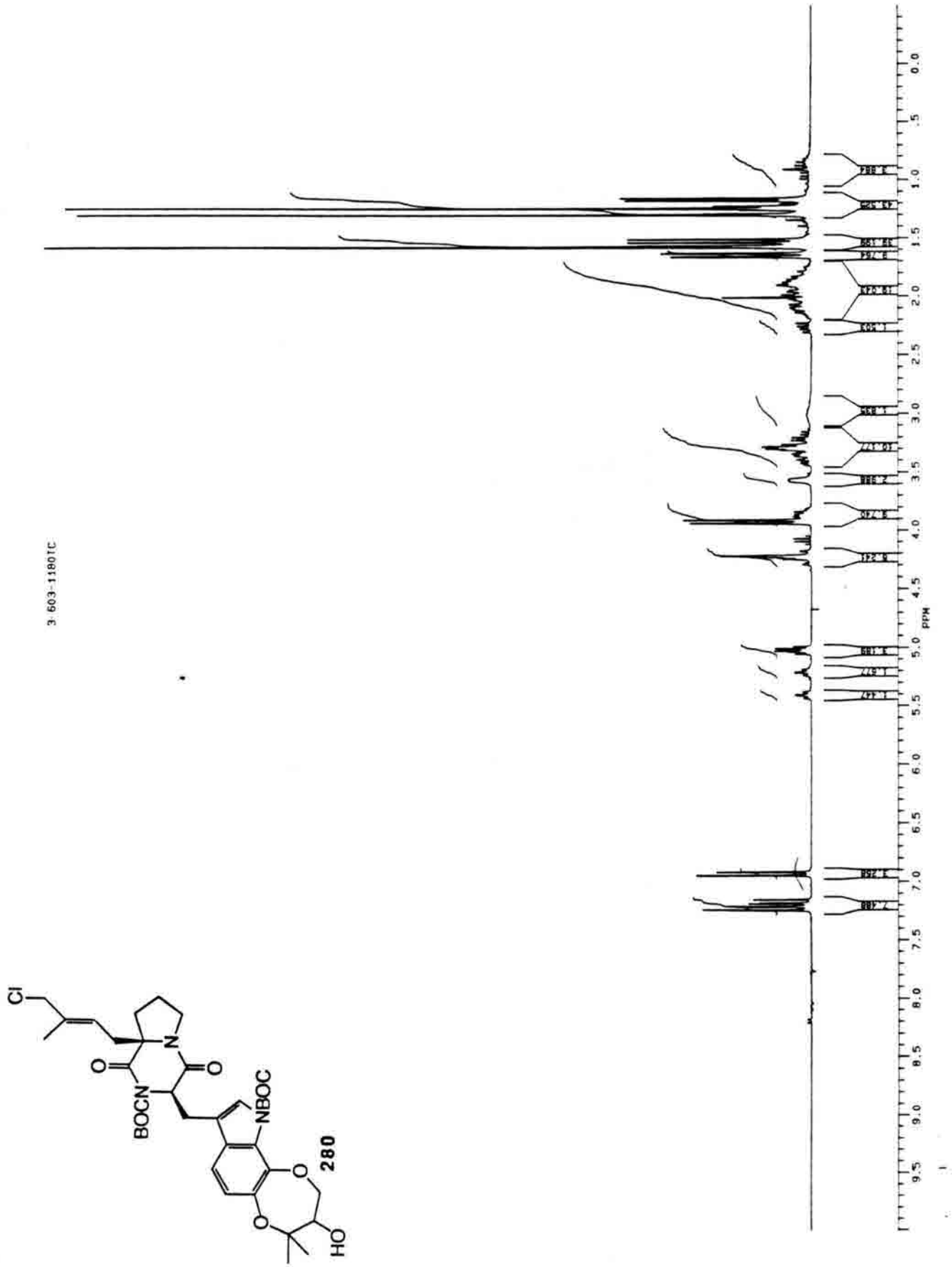
To a stirred solution of **279** (50.0mg, 0.0725mmol, 1.0eq) in DMF (0.73mL) at 0 °C, under Ar was added collidine (0.014mL, 0.109mmol, 1.5eq) and LiCl (5.27mg, 0.123mmol, 1.7eq). After 15 minutes MsCl (8.4μL, 0.109mmol, 1.5eq) was added and the reaction allowed to reach room temperature in the course of 16 hours. At this time an additional amount (1.0eq) of each reagent was added in the same manner as before. After 8.5 hours there was little change by TLC so a large excess of MsCl (0.06mL, 0.775mmol, 10.7eq) was added at 0 °C and stirred ≈12 hours until only the desired product was apparent by TLC. The solution was diluted with 1:1 hexane/ethyl acetate, washed with water, brine, dried over $MgSO_4$ and concentrated. chromatography; radial, 1:1 ethyl acetate/hexanes. The product was obtained as a foamy glass. yield; 45.5mg, 91%.

^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.18 (3H, s); 1.24 (9H, s); 1.30 (9H, s); 1.51 (3H, s); 1.54 (3H, s); 1.58 (18H, s); 1.64 (3H, s); 1.66 (3H, s); 1.74–2.18 (11H, m); 2.27 (2H, dd, J = 8.1, 15.0Hz); 3.02 (2H, br s, D_2O exch.) 3.19 (2H, dd, J = 7.2, 14.8Hz); 3.27–3.44 (4H, m); 3.56 (2H, br s); 3.81–3.89 (2H, m); 3.91 (2H,

s); 3.94 (2H, s); 4.18–4.30 (4H, m); 4.99–5.06 (2H, m); 5.21 (1H, t, J = 8.3Hz); 5.38–5.43 (1H, m); 6.93 (2H, d, J = 8.3Hz); 7.17 (1H, d, J = 8.3Hz); 7.20 (1H, d, J = 8.3Hz); 7.21 (1H, s); 7.24 (1H, s).

IR (neat) 3384, 2920, 1750, 1736, 1657, 1367, 1250, 1149 cm^{-1}.

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N
O
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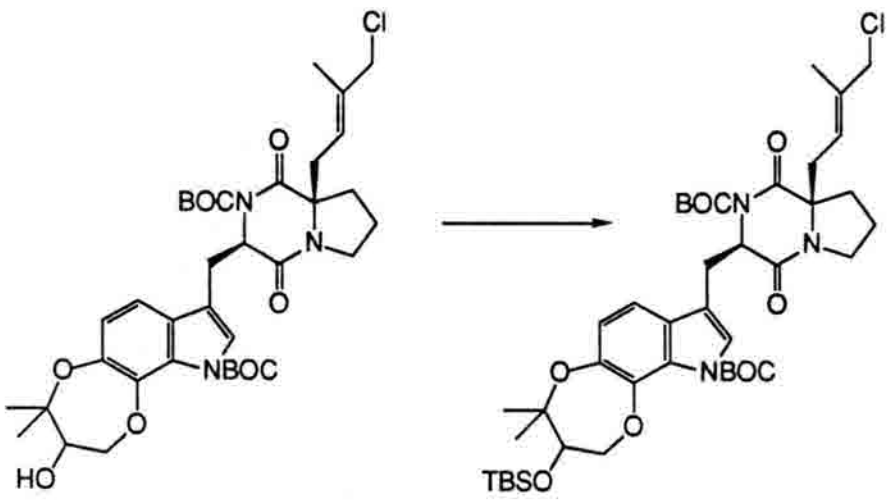
NBOC
O
O
HO
280



280 **281**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[2-[(1,1-dimethylethoxy)carbonyl]-8a-[4-chloro-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino-[2,3-g]indole-10-carboxylate (281)

To a stirred solution of **280** (96.2mg, 0.37mmol, 1.0eq) in CH_2Cl_2 (0.5mL) under Ar was added 2,6-lutidine (0.016mL, 0.137mmol, 1.0eq) and t-BDMSOTf (0.031mL, 0.137mmol, 1.0eq). After 1 hour an additional amount (0.5eq) of the two reagents was added. One hour later another portion (0.5eq) of each reagent was added. The solution was stirred for 75 more minutes. It was then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. chromatography; radial, 1:2 ethyl acetate/hexanes, yield; 106.5mg, 99%

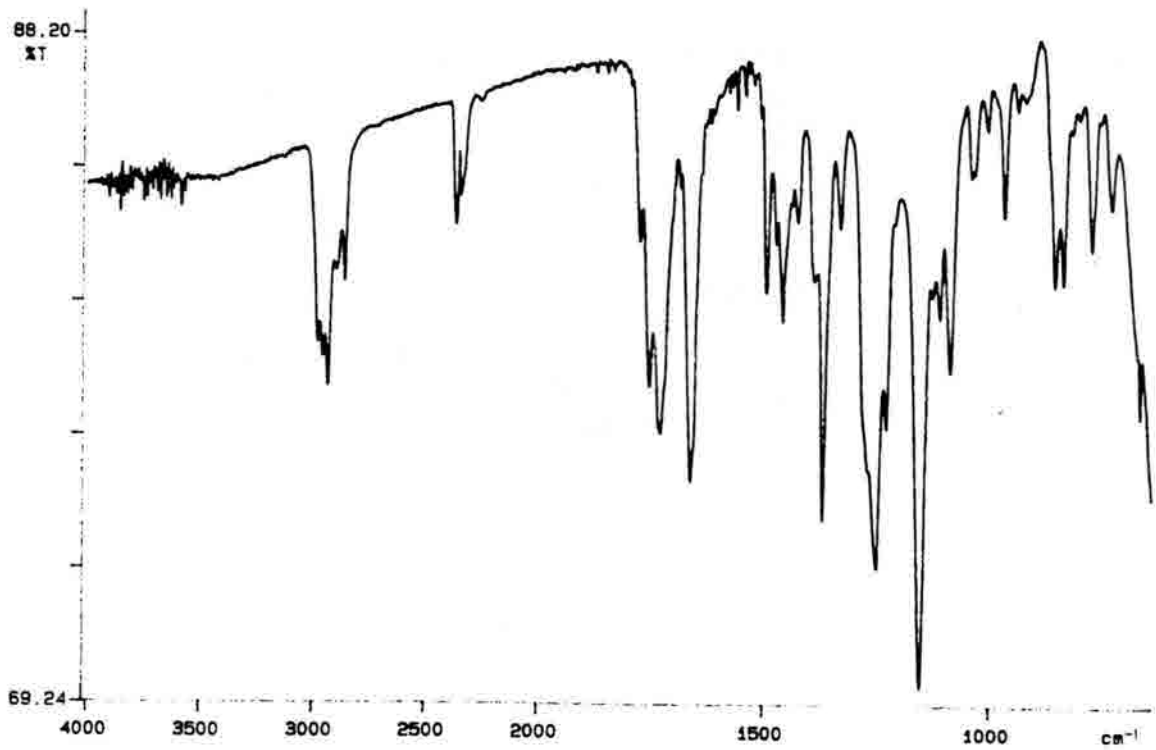
^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.10 (3H, s); 0.11 (6H, s); 0.12 (3H, s); 0.877 (18H, s); 1.04 (3H, s); 1.06 (3H, s); 1.22 (9H, s); 1.29 (9H, s); 1.44 (3H, s); 1.46 (3H, s); 1.58 (18H, s); 1.62 (3H, s); 1.65 (3H, s); 1.76–2.13 (8H, m); 2.22 (2H, dd, J = 8.4, 14.8Hz); 3.19 (2H, dd, J = 7.1, 14.7Hz): 3.26–3.42 (4H, m); 3.68–3.78 (2H, m); 3.81–3.87 (4H, m); 3.90 (2H, s); 3.94 (2H, s); 4.10–4.17 (2H, m); 5.00–5.05 (2H, m); 5.22 (1H, t, J = 7.6Hz); 5.41 (1H, t, J = 7.6Hz); 6.91 (2H, d, J = 8.3Hz); 7.14 (1H, d, J = 8.3Hz); 7.16 (1H, d, J = 8.3Hz); 7.21 (1H, s); 7.24 (1H, s).

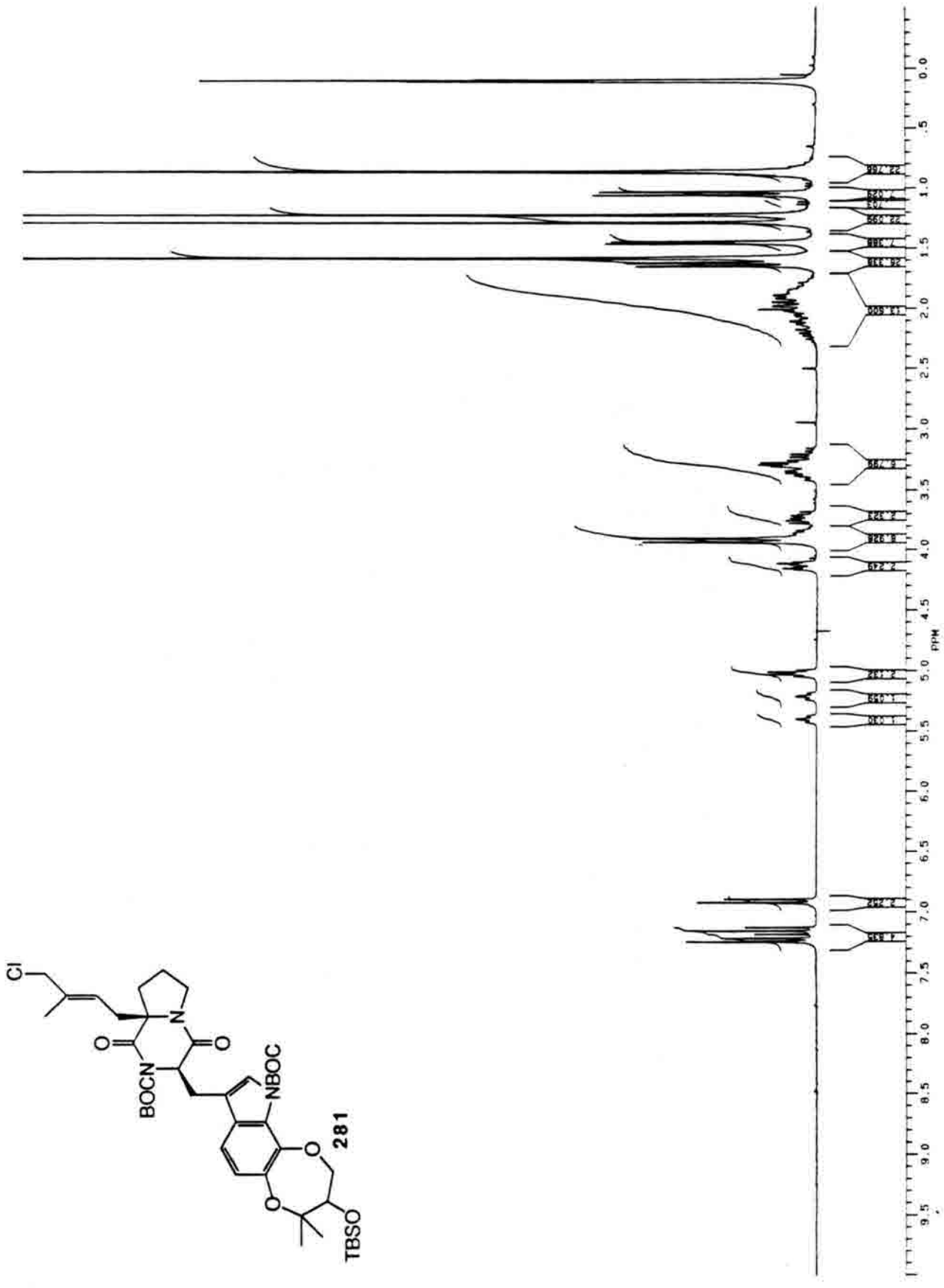
^{13}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ –5.04, –4.11, –4.05, 14.28, 17.75, 18.25, 19.75, 19.83, 25.64, 27.33, 27.41, 27.92, 28.49, 29.60, 30.10, 34.47, 34.68, 36.08, 45.20, 45.32, 51.32, 51.36, 60.51, 68.07, 68.15, 70.86, 70.93, 75.72, 80.19, 83.05, 84.17, 84.20, 113.56, 113.82, 114.10, 114.20, 120.03, 120.11, 122.64, 122.68, 126.90, 127.05, 127.84, 127.92, 129.04, 135.63, 135.83, 140.43, 146.28, 146.41, 148.31, 148.36, 150.34, 150.49, 164.36, 164.50, 168.64, 168.67.

IR (neat) 2936, 1754, 1729, 1663, 1496, 1456, 1370, 1248, 1152, 1086, 838 cm^{-1}.

EI HRMS 815.3973 ($C_{42}H_{62}N_3O_9SiCl$ requires 815.3944).

m.p. 70–73 °C, white crystalline solid.

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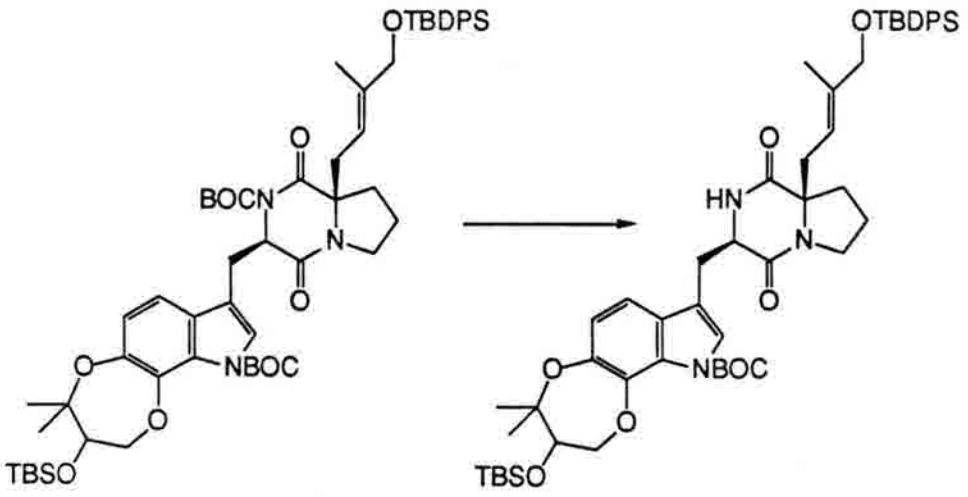
NBOC
O
O
O
TBSO
281
PPM



278 **284**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[-8a-[4-[[1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (208)

To a flask fitted with a reflux condenser was added the fully protected **278** (799mg, 0.771mmol, 1.0eq). This was followed by CH_3CN (15.4mL) and dimethylamine (0.53mL, 3.85mmol 5.0eq, 40% solution in water) The resulting solution was refluxed for 2h and 20min. The solvent was removed and the remaining oil subjected to chromatography. chromatography; radial, 1:2 ethyl acetate/hexanes. yield; 657mg, 92%. An analytical sample was obtained by PTLC, 1:2 ethyl acetate/hexanes, (white foamy oil). ^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.14 (6H, s); 0.23 (6H, s); 0.88 (18H, s); 1.01 (18H, s); 1.10 (6H, s); 1.48 (6H, d); 1.59 (18H, s); 1.62 (6H, s); 1.98–2.05 (6H, m); 2.07–2.19 (2H, m); 2.37–2.47 (2H, m); 2.64–2.75 (2H, m); 2.94 (2H, dd, J = 11.6, 14.1Hz); 3.41–3.47 (4H, m); 3.82 (2H, dd, J = 9.6, 12.2Hz); 3.93–4.03 (4H, m); 4.07 (4H, br s); 4.10–4.15 (4H, m); 4.20 (2H, dd, J = 2.7, 12.4Hz); 5.56–5.61 (2H, m); 5.78 (1H, d, J = 3.0Hz, D_2O exch.); 5.81 (1H, d, J = 2.8Hz, D_2O

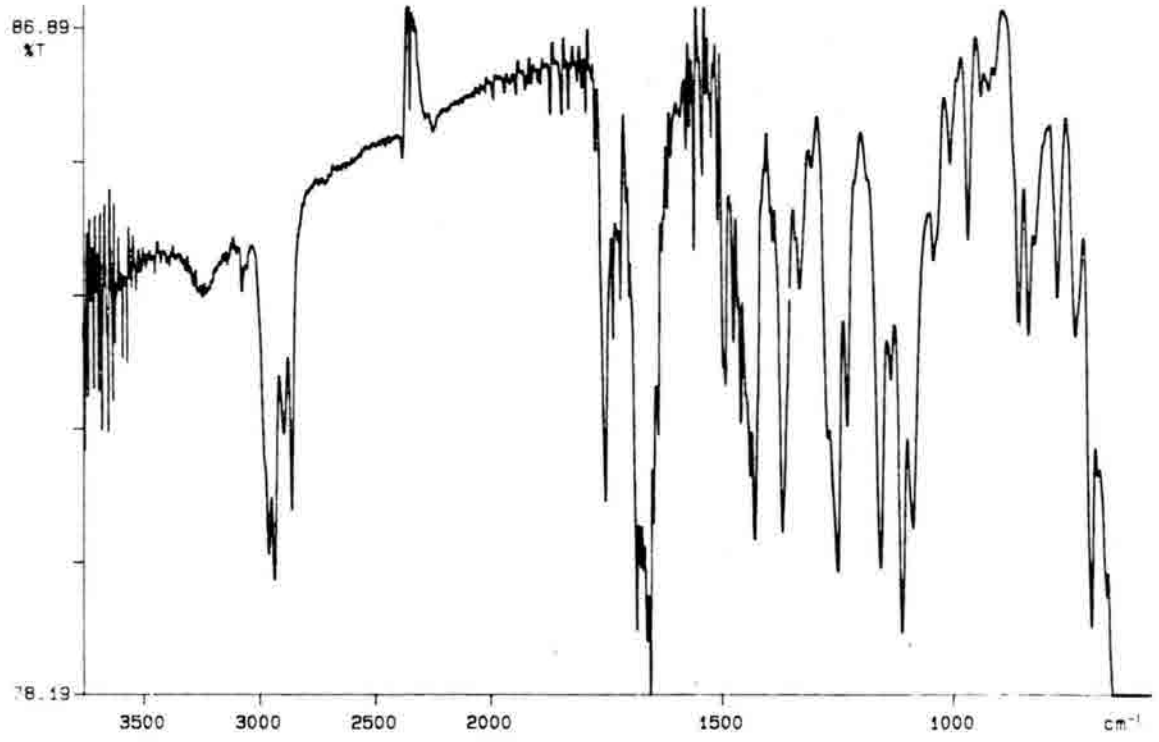
exch.); 6.877 (1H, d, J = 8.4Hz); 6.884 (1H, d, J = 8.4Hz); 7.09 (2H, d, J = 8.4Hz); 7.20–7.40 (14H, m); 7.56 - 7.61 (8H, m).

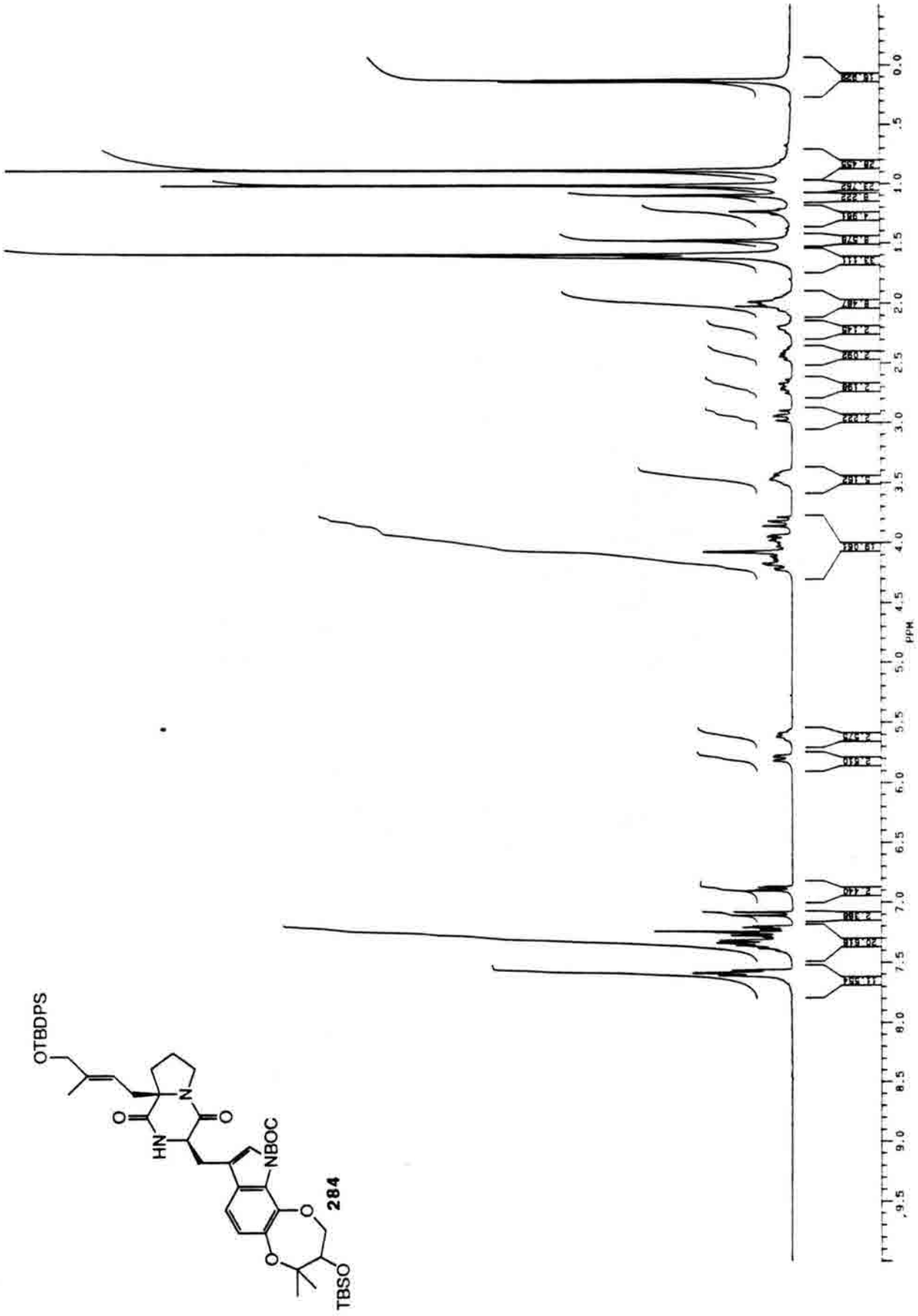
^{13}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) d – 5.00, –4.06, 13.68, 14.01, 17.78, 18.63, 18.77, 19.12, 19.60, 22.52, 25.67, 26.74, 27.96, 28.38, 28.44, 31.45, 31.62, 31.69, 34.93, 35.82, 44.81,57.46, 67.47, 68.20, 7099, 75.78, 76.57, 77.00, 77.42, 80.34, 83.34, 83.14, 113.32, 114.62, 116.64, 120.14, 126.28, 126.33, 127.54, 127.56, 128.13, 128.24, 128.38, 128.41, 128.55, 133.12, 133.20, 135.37, 139.23, 140.48, 140.55, 146.44, 146.53, 148.42, 164.38, 169.65, 169.68.

IR (neat) 3246, 2960 2861, 1750, 1676, 1662, 1430, 1366, 1252, 1159, 1109, 1090 cm^{-1}.

EI HRMS 935.48955 ($C_{53}H_{73}N_3O_8Si_2$ requires 935.4936).

microanalysis cacl'd for $C_{53}H_{73}N_3O_8Si_2$: C, 67.57; H, 7.96; N, 4.54 Found: C, 67.62; H, 7.94; N, 4.32.

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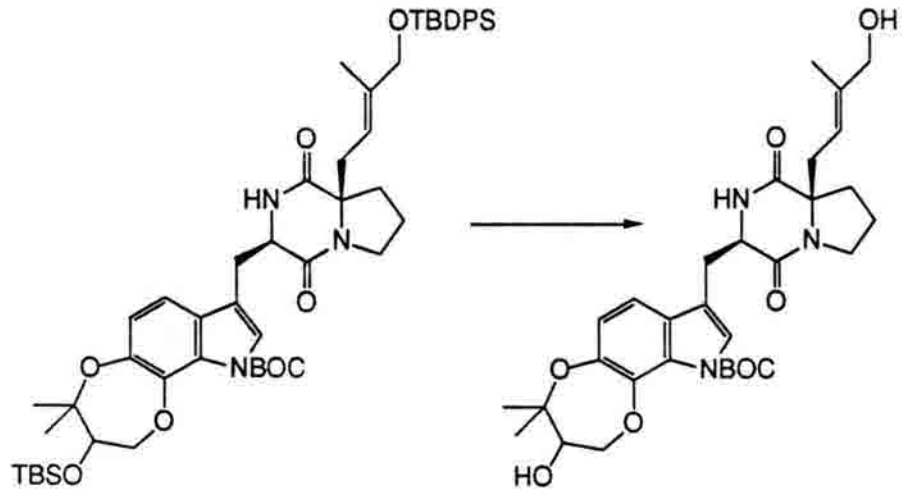
284
PPM



284 **285**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[-8a-[4-hydroxy-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-4,4-dimethyl-3-hydroxy-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (285)

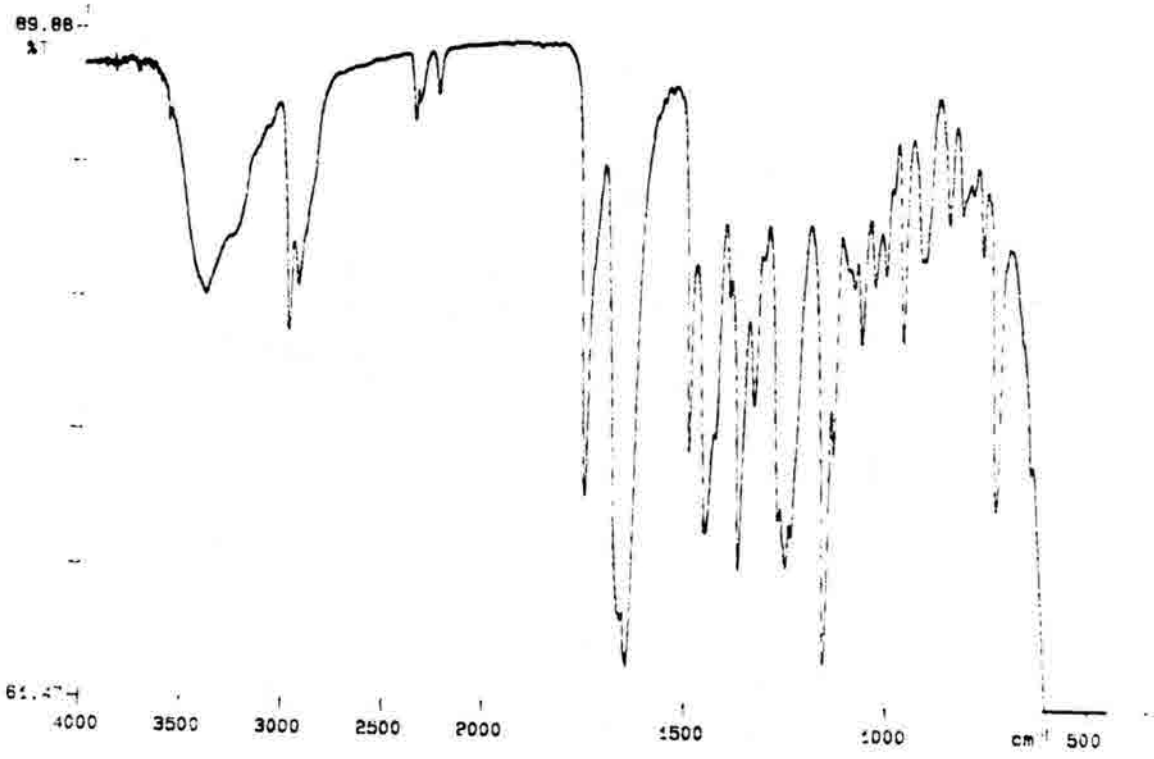
To a stirred solution of **278** (46.8mg, 0.0802mmol, 1.0eq) at 0°C, under Ar, in THF (0.33mL) was added n-Bu_4NF (0.2mL, 0.20mmol, 2.5eq, 1.0M/THF) dropwise. After the addition was complete, the ice bath was removed, and the reaction continued for two hours. The solution was then diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; radial, ethyl acetate, (white solid). yield; 24.7mg, 85%.

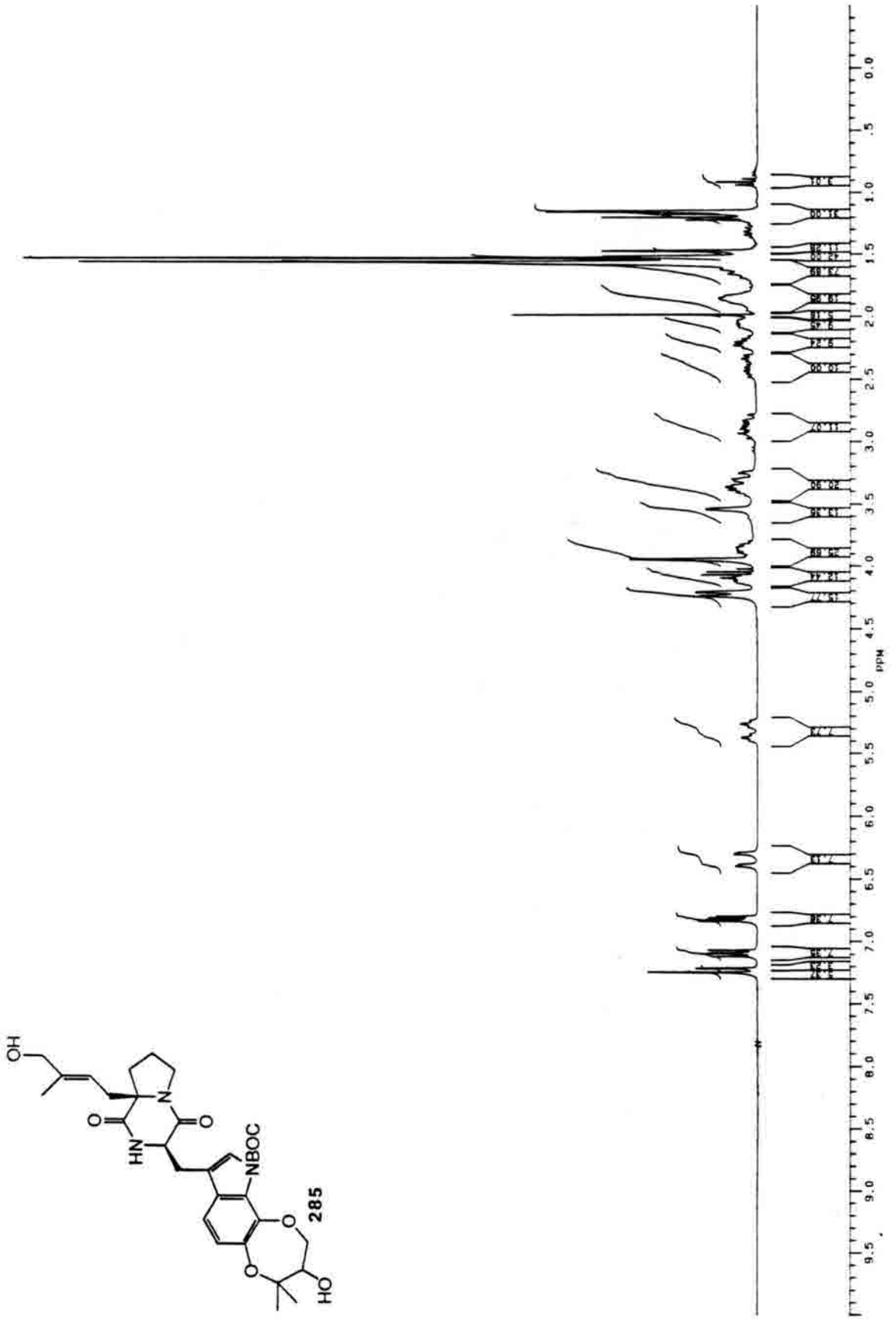
^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.20 (6H, s); 1.55 (3H, s); 1.56 (3H, s); 1.60 (9H, s); 1.61 (9H, s); 1.63 (3H, s); 1.65 (3H, s); 1.73–2.00 (4H, m, 2H D_2O exch.); 2.15–2.20 (2H, m); 2.28–2.42 (3H, m); 2.58 (1H, dd, J = 8.1, 14.3Hz); 2.88–3.03 (2H, m); 3.18 (1H, d, J = 11.4Hz, D_2O exch.); 3.23 (1H, d, J = 11.4Hz, D_2O exch.); 3.34–3.50 (4H, m); 3.59 (2H, d, J = 11.6Hz); 3.93–4.04 (6H, m); 4.11–4.25 (2H, m); 4.28–4.29 (4H, m); 5.30 (1H, m); 5.46 (1H, m); 5.79 (1H, d, J = 2.8Hz, D_2O exch.); 5.82 (1H, d, J = 2.9Hz, D_2O exch.); 6.91 (1H, d, J = 8.3Hz); 6.92 (1H, d, J = 8.4Hz); 7.15 (1H, d, J = 8.3Hz); 7.16 (1H, d, J = 8.3Hz); 7.31 (2H, s).

IR (neat) 3389 (br) 2981, 1754, 1643, 1493, 1454, 1369, 1329, 1244, 1154, 967, 729 cm^{-1}.

EI HRMS 583.2873 ($C_{31}H_{41}N_3O_8$ requires 583.2894)

m.p. 107–111 °C.

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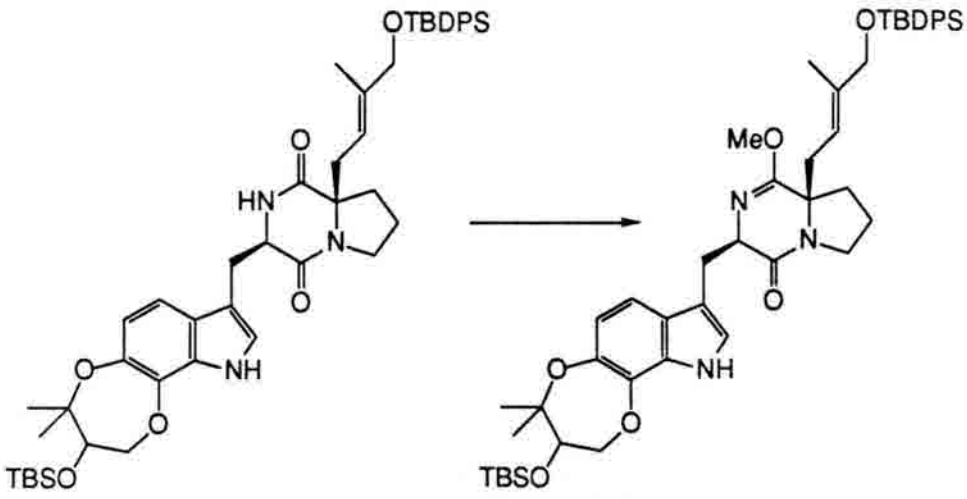
O
O
HN
NBOC
O
O
HO
285
ppm



273 **275**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-[4-[[1,1-dimethyl-ethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (275)

To a stirred solution of **273**(3.87g, 4.63mmol, 1.0eq) in CH_2Cl_2 (46mL) under Ar, at 0 °C was added Na_2CO_3 (9.8g, 92.6mmol, 20.0eq). After 10 minutes Me_3OBF_4 (3.42g, 23.15mmol, 5.0eq) was added in one portion. The mixture was stirred for 4.0 hours at room temperature, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; flash column, 1:2 hexanes/ethyl acetate, 1:1 hexanes/ethyl acetate. yield; 3.20g, 81%. An analytical sample was obtained by PTLC, ethyl acetate, (white foamy solid).

^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.120 (12H, s); 0.875 (18H, s); 1.02 (18H, s); 1.06 (3H, s); 1.07 (3H, s); 1.45 (12H, s); 1.65–2.08 (12H, m); 3.07–3.15 (2H, m); 3.26 (2H, dd, J = 6.2, 12.6Hz); 3.32–3.40 (2H, m); 3.61 (6H, s); 3.70–3.86 (2H, m); 3.91–3.95 (4H, m); 3.99 (2H, s); 4.15 (2H, dd, J = 3.6, 11.7Hz); 4.36–4.40 (2H, m); 5.37–5.44 (2H, br m); 6.69 (2H, d, J = 8.4Hz); 7.01 (2H, d, J =

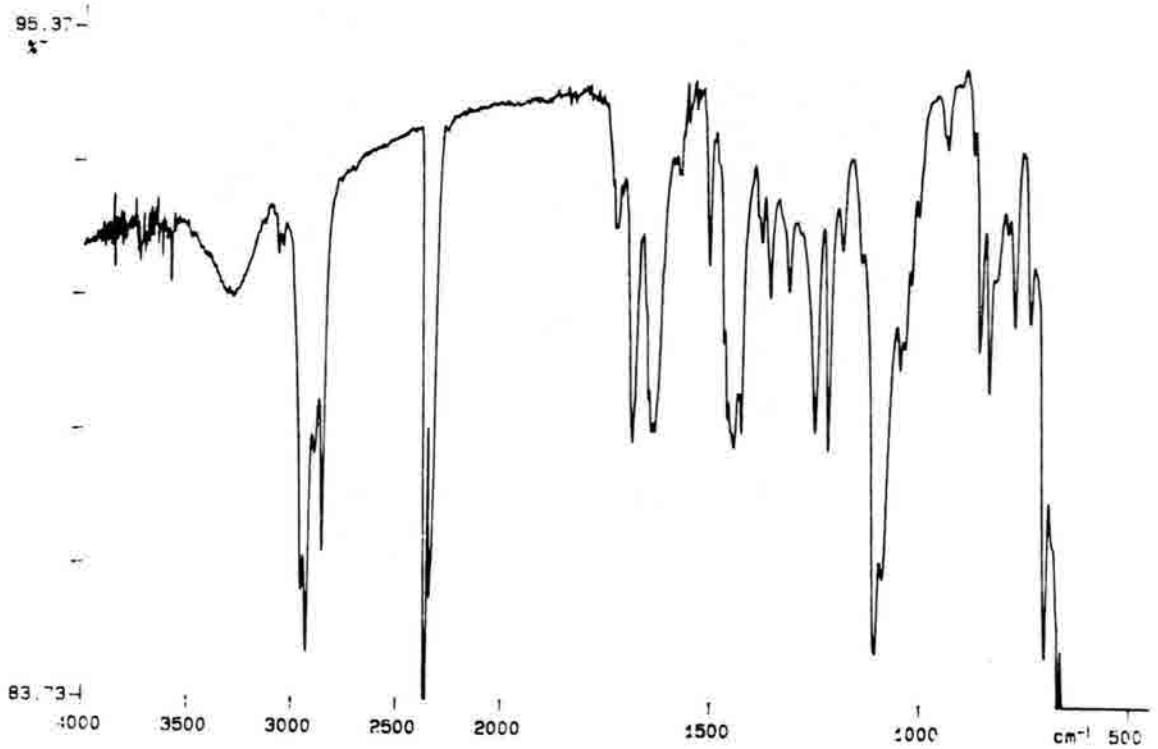
1.7Hz); 7.15 (2H, d, J = 8.4Hz); 7.26–7.41 (12H, m); 7.58–7.62 (8H, m); 8.06 (2H, s, D_2O exch.).

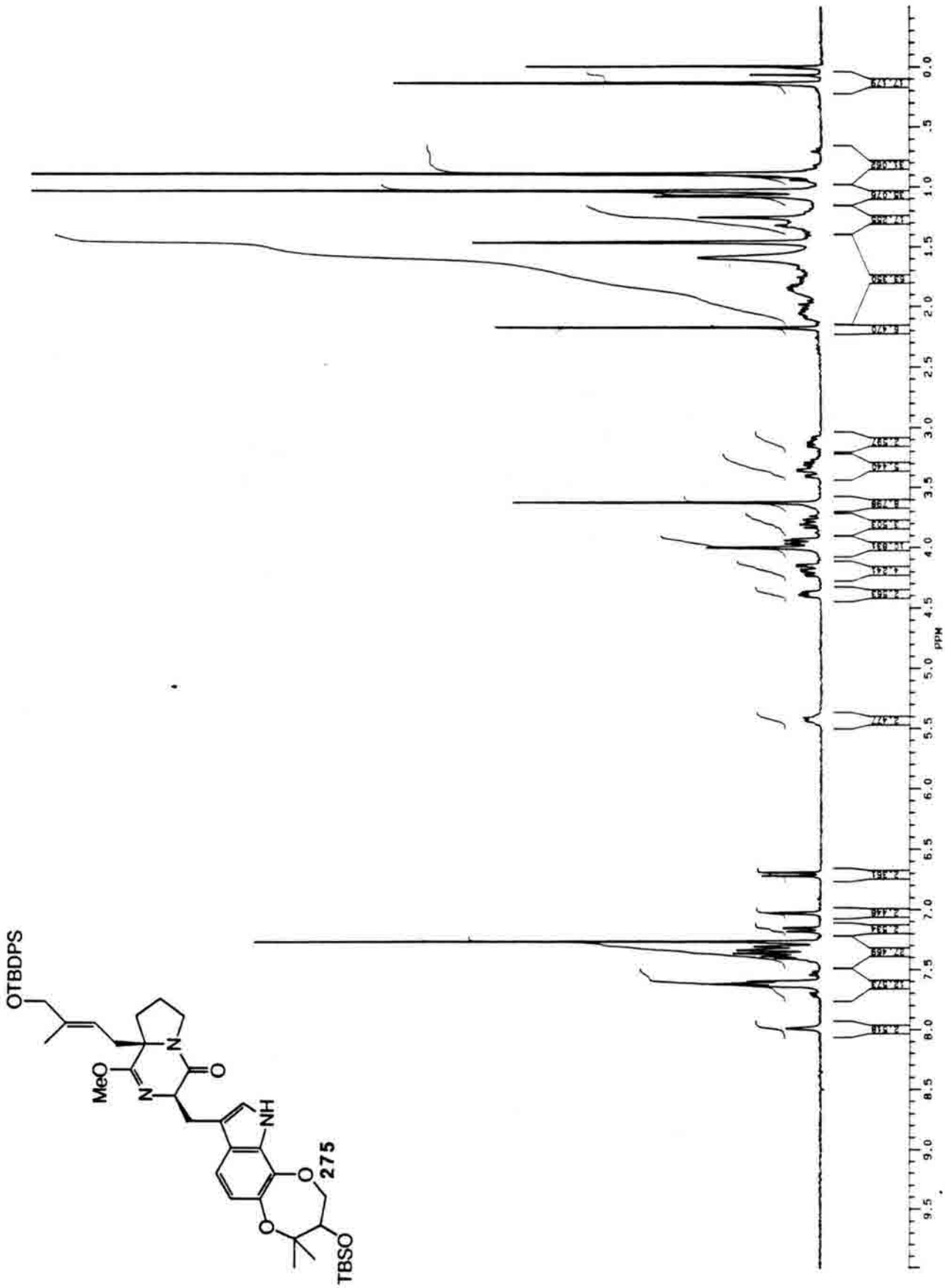
IR (neat) 3292, 2932, 1687, 1643, 1447, 1251, 1218, 1109, 837 cm^{-1}.

MS (EI) 849 *m/e* (rel intensity) 849 (M^+, 8.9) 361 (26) 360 (95) 167 (100).

microanalysis calc'd. for $C_{49}H_{67}N_3O_6Si_2$: C, 69.02; H, 7.94; N, 4.94; Found: C, 69.02; H, 7.88; N, 4.79.

m.p. 74–76 °C.




OTBDPS
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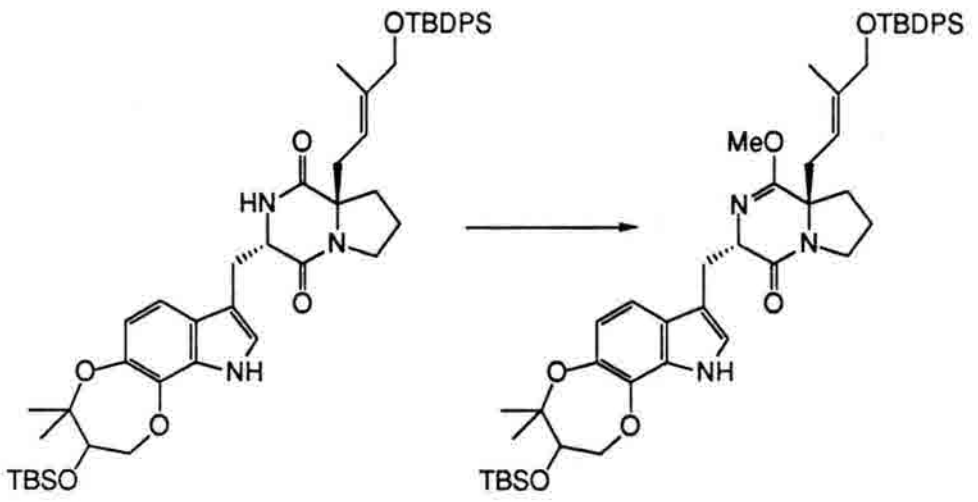
N
N
O
NH
O
O
O
TBSO
275
PPM



274 **292**

[3α,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-[4-[[1,1-dimethyl-ethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indole-10-carboxylate (292)

To a stirred solution of **274** (8.47g,10.13mmol, 1.0eq) in CH_2Cl_2 (101mL) at 0 °C, under Ar was added Na_2CO_3 (21.26g, 202.6mmol, 20.0eq). After 15 minutes Me_3OBF_4 (7.49g, 50.64mmol, 5.0eq) was added in one portion. Five minutes later the ice bath was removed, and the reaction stirred for 4.5 hours. It was then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; column, yield; 5.30g, 62%.{The yield of **292** was 365mg (71%) from 508mg of **274**}. An analytical sample was obtained by PTLC, 1:2 ethyl acetate/hexanes, (white crystalline solid).

^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.13 (3H, s); 0.14 (9H, s); 0.89 (18H, s); 1.03 (9H, s); 1.04 (9H, s); 1.087 (3H, s); 1.093 (3H, s); 1.28–1.43 (3H, m); 1.48 (3H, s); 1.50 (6H, s); 1.79–1.89 (4H, m); 2.24–2.38 (4H, m); 3.22–3.42 (6H, m); 3.60 (3H, s); 3.62 (3H, s); 3.68–3.76 (2H, m); 3.79–3.87 (2H, m); 3.94 (2H, d, J = 3.4Hz); 3.97 (4H, br s); 4.15–4.20 (2H, m); 4.26–4.32 (2H, m); 5.41 (2H, t, J = 7.8Hz);

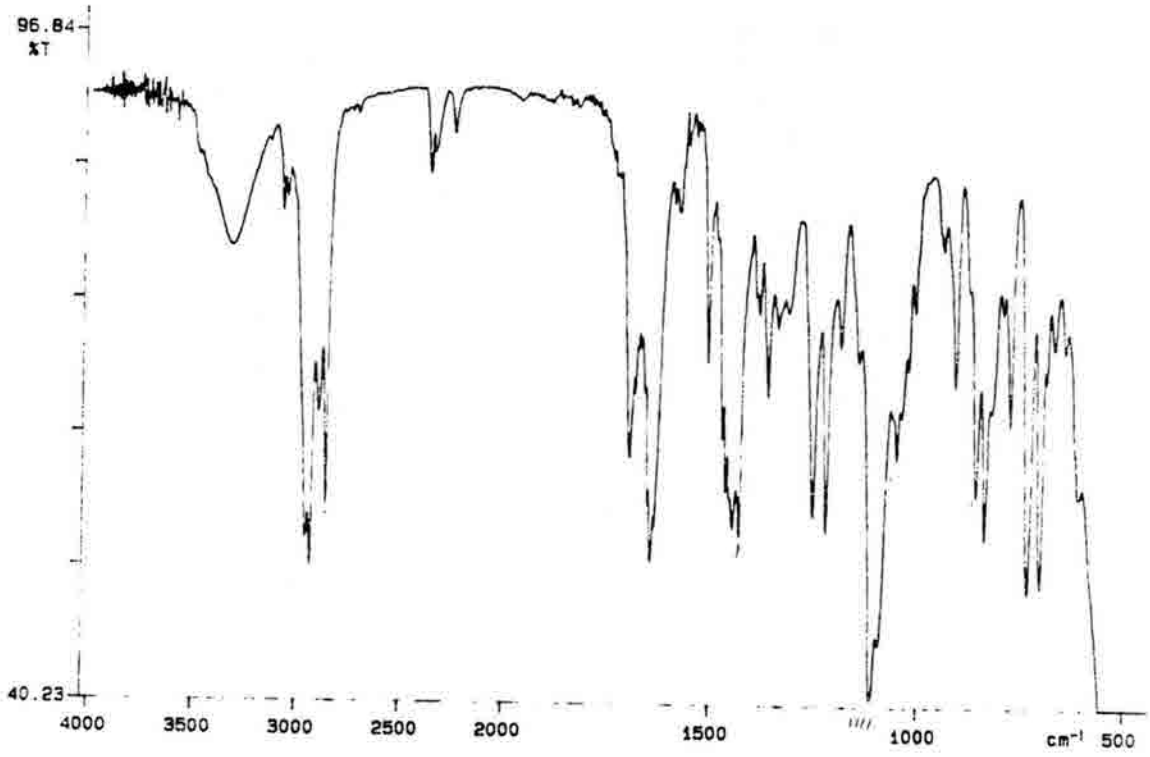
6.701 (1H, d, J = 8.5Hz); 6.703 (2H, d, J = 8.4Hz); 6.96 (1H, d, J = 2.6Hz); 6.97 (1H, d, J = 2.6Hz); 7.28 (2H, d, J = 8.5Hz); 7.32–7.44 (12H, m); 7.60–7.64 (8H, m); 7.97 (2H, br s, D_2O exch.).

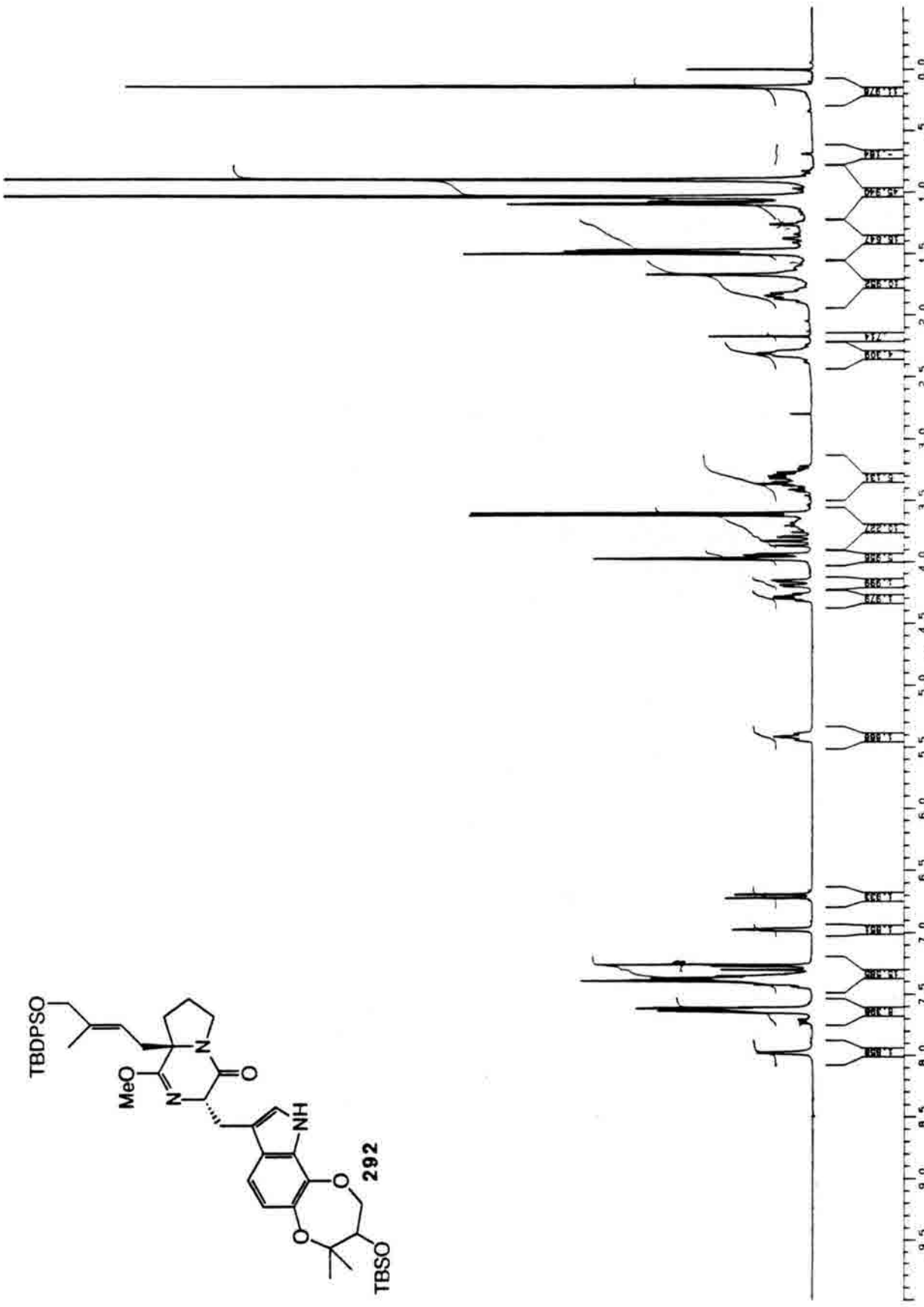
IR (neat) 3304, 2930, 1695, 1645, 1447, 1249, 1221, 836 cm^{-1}.

EI HRMS 849.4550 ($C_{49}H_{67}N_3O_6Si_2$ requires 849.4568)

microanalysis calc'd. for $C_{49}H_{67}N_3O_6Si_2$: C, 69.22; H, 7.94; N, 4.94 found: C, 59.06; H, 8.04; N, 4.89.

m.p. 54–58 °C.

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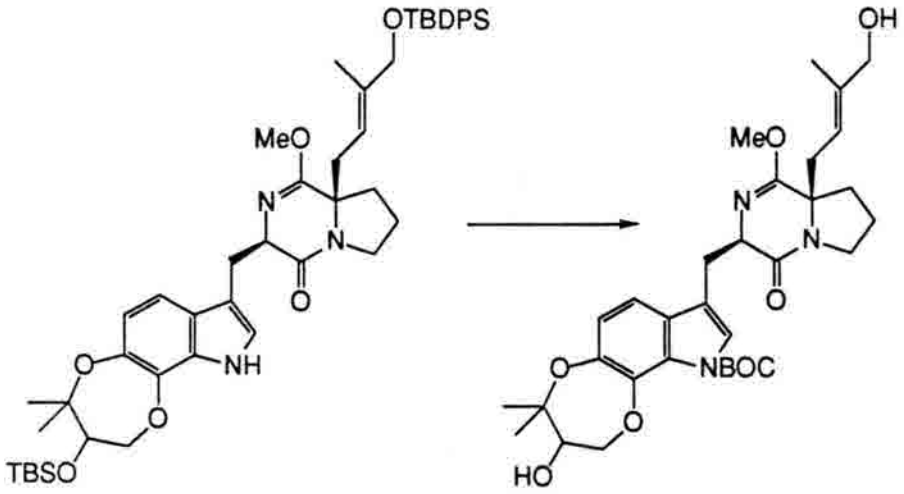
N
N
O
NH
O
O
TBSO
292
PPM



275 **276**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-(4-hydroxy-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g] indole-10-carboxylate (276)

To stirred solution of **275** (5.45g, 6.41mmol, 1.0eq) in CH_2Cl_2 (32mL) under Ar at 0 °C was added Et_3N (0.89mL, 6.41mmol, 1.0eq) and DMAP (783.1mg, 6.41mmol, 1.0eq). After 10 minutes $(BOC)_2O$ (4.20g, 19.2mmol, 3.0eq) was added in one portion. The reaction was stirred for 6 hours and diluted with THF (45mL). The remaining CH_2Cl_2 was removed by evaporation (until the volume in the flask was 45mL). The flask was charged with n-Bu_4NF (19.2mL, 19.2mmol, 3.0eq, 1.0M/THF) and stirred at room temperature for approx. 12 hours. The solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; column, 1:2 ethyl acetate/hexanes and 2:1 ethyl acetate/hexanes. yield; 3.45g, 90%. { The yield of **276** was 243mg (97%) from 355mg of **275**}. An analytical sample was obtained by PTLC, 2:1 ethyl acetate/hexanes, (white foamy solid).

^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.18 (6H, s); 1.52 (3H, s); 1.53 (1H, s); 1.56 (1H, s); 1.57 (21H, s); 1.61–2.07 (10H, m); 2.14 (2H, dd, J = 8.6,

14.5Hz); 2.85 (2H, br s, D_2O exch.); 2.92–3.01 (2H, m); 3.18–3.35 (6H, m); 3.56 (2H, br s, D_2O exch.); 3.62 (3H, s); 3.64 (3H, s); 3.88 (4H, br s); 3.91–4.00 (2H, m); 4.25 (4H, br s); 4.30–4.39 (2H, m); 4.98–5.01 (2H, m); 6.87 (1H, d, J = 8.3Hz); 6.88 (1H, d, J = 8.3Hz): 7.16 (1H, d, J = 8.3Hz); 7.17 (1H, d, J= 8.3Hz); 7.34 (1H, s); 7.35 (1H, s).

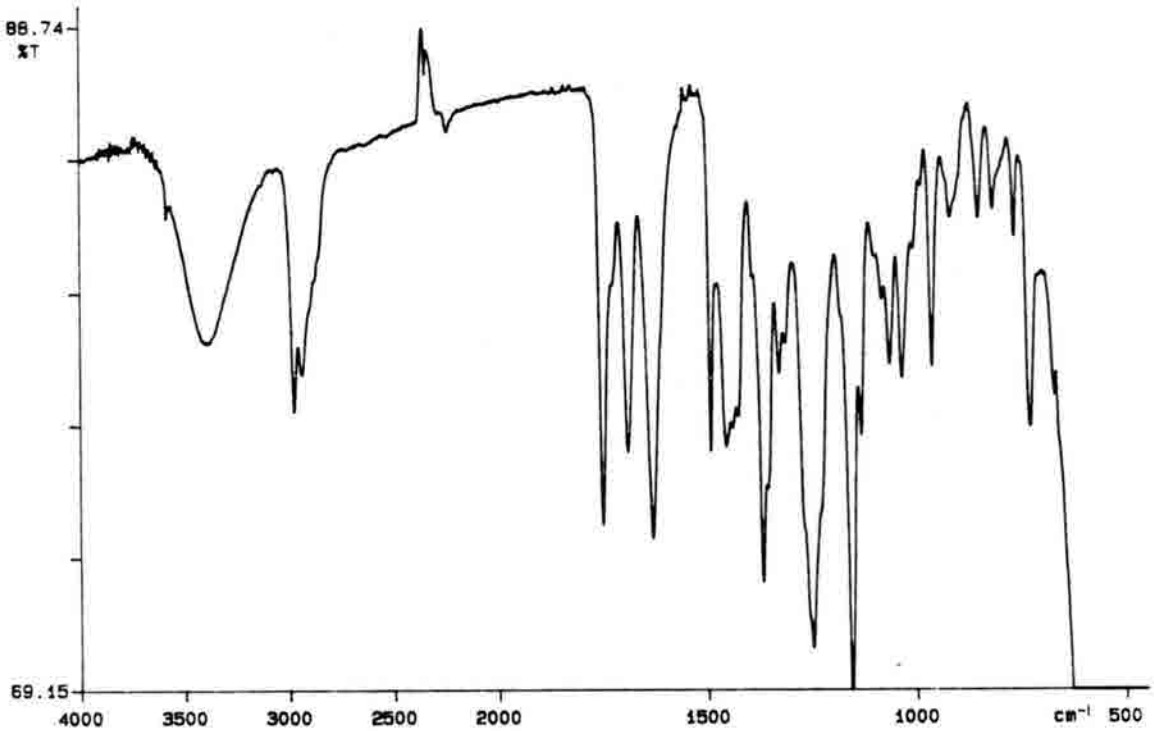
^{13}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 13.44, 19.47, 19.68, 23.51, 23.63, 25.13, 25.32, 27.86, 30.34, 30.52, 34.38, 34.84, 35.12, 35.26, 43.38, 43.63, 52.63, 52.70, 62.03, 62.40, 65.26, 65.45, 67.67, 67.76, 70.63, 75.37, 82.57, 82.64, 114.53, 114.73, 116.75, 116.88, 118.18, 118.32, 119.04, 119.12, 126.34, 128.04, 128.10, 129.94, 130.07, 138.64, 138.71, 140.68, 146.15, 148.49, 161.32, 161.50, 168.53, 168.66

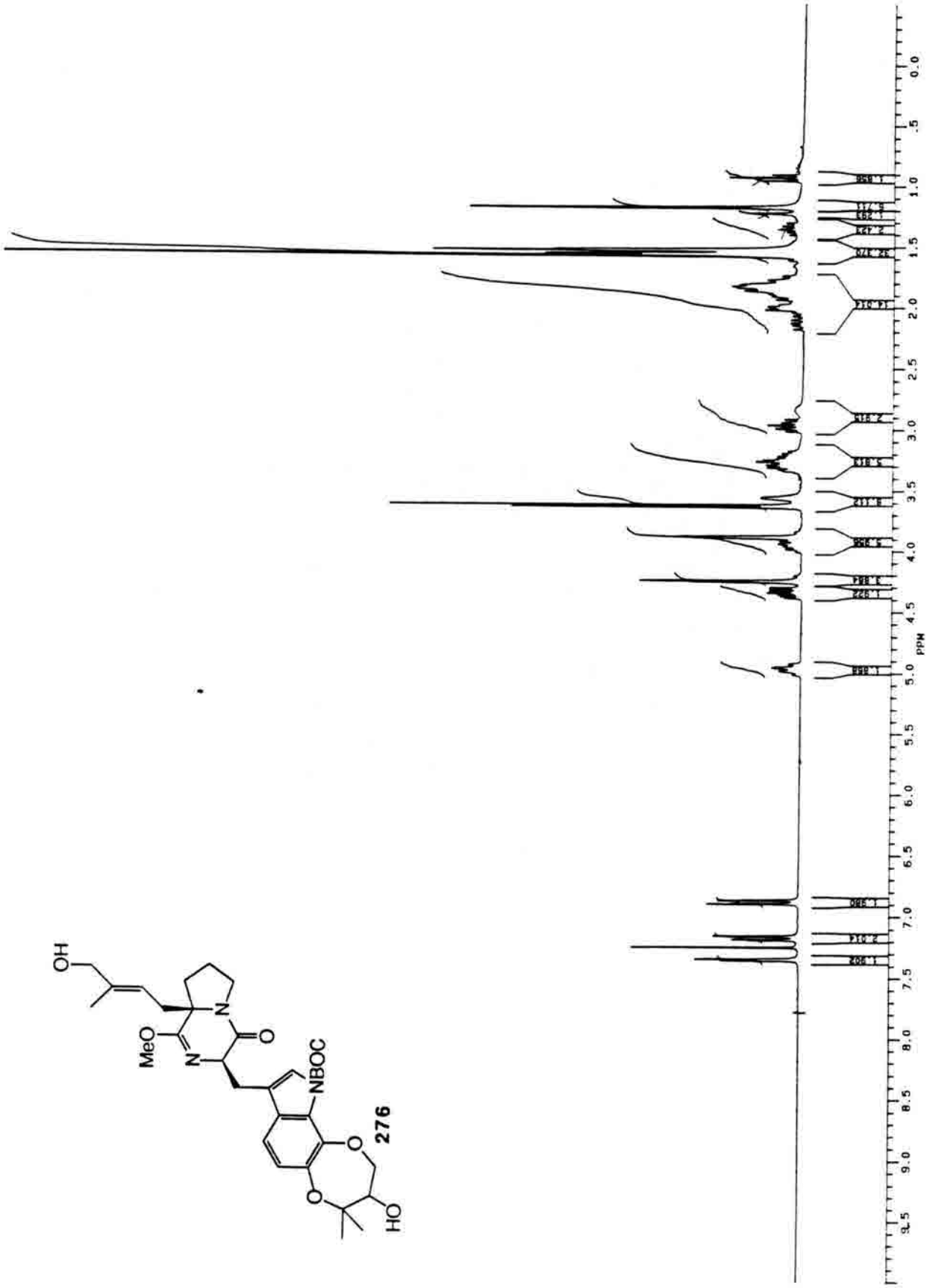
IR (neat) 3390 (br), 2976, 1752, 1692, 1632, 1491, 1453, 1371, 1251, 1158, 733 cm^{-1}.

microanalysis calc'd. for $C_{32}H_{43}N_3O_8$: C, 64.30; H, 7.25; N, 7.03; found: C, 64.12; H, 7.41; N, 6.88.

EI HRMS m/e 597.3065 ($C_{32}H_{43}N_3O_8$ requires 597.3050).

m.p. 72–85 °C.

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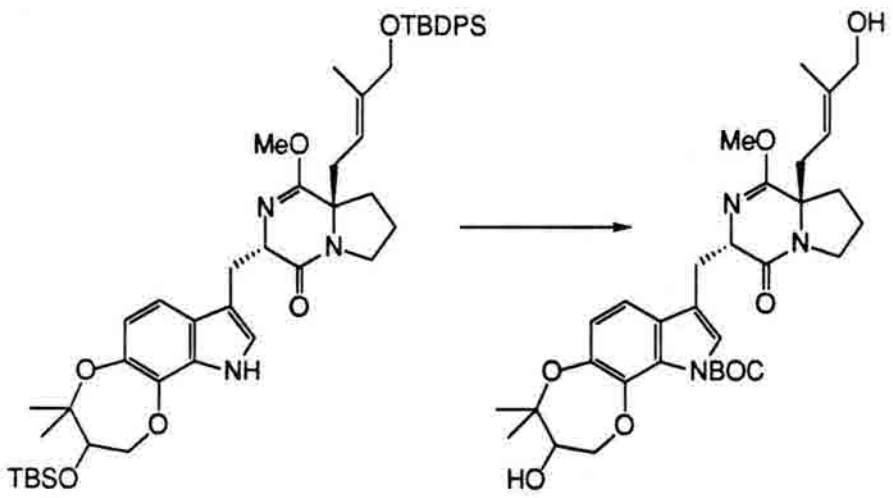
N
O
NBOC
O
O
HO
276
PPM



292 **293**

[3α,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-(4-hydroxy-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g] indole-10-carboxylate (293)

To a stirred solution of **292** (5.30g, 5.65mmol, 1.0eq) under Ar in CH_2Cl_2 (1.5mL) at 0 °C was added Et_3N (0.79mL, 5.65mmol, 1.0eq) and DMAP (689.7mg, 5.65mmol, 1.0eq). After 5 minutes $(BOC)_2O$ (3.70g, 16.94mmol, 3.0eq) was added in one portion. The reaction was stirred for 4.5 hours and diluted with THF (40mL). The remaining CH_2Cl_2 was removed by evaporation (until the volume in the flask was 40mL). The flask was charged with n-Bu_4NF (17.0mL, 17.0mmol, 3.0eq, 1.0M/THF) and stirred at room temperature for ≈12 hours. The solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; column, ethyl acetate, yield; 3.16g, 85%. {the yield of **293** was 179mg (98%) with 260mg of **292**}

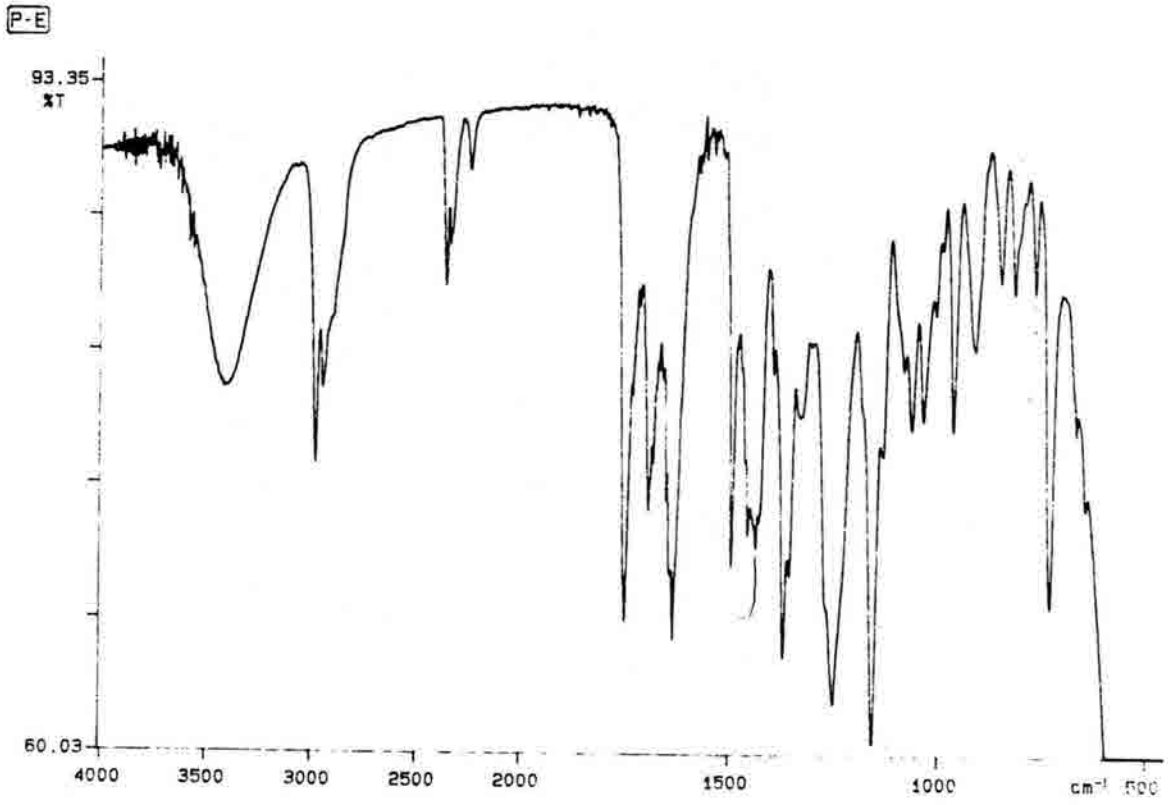
^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.16 (3H, s); 1.18 (3H, s); 1.51 (3H, s); 1.52 (3H, s); 1.55 (6H, s); 1.57 (18H, s); 1.60–2.14 (10H, m, 2H D_2O exch.);2.22–2.37 (4H, m); 3.06–3.18 (3H, m, 1H D_2O exch.); 3.26–3.36 (5H, m, 1H D_2O exch.); 3.55 (3H, s); 3.56 (2H, br s); 3.60 (3H, s); 3.63–3.72 (2H, m); 3.89 (4H,

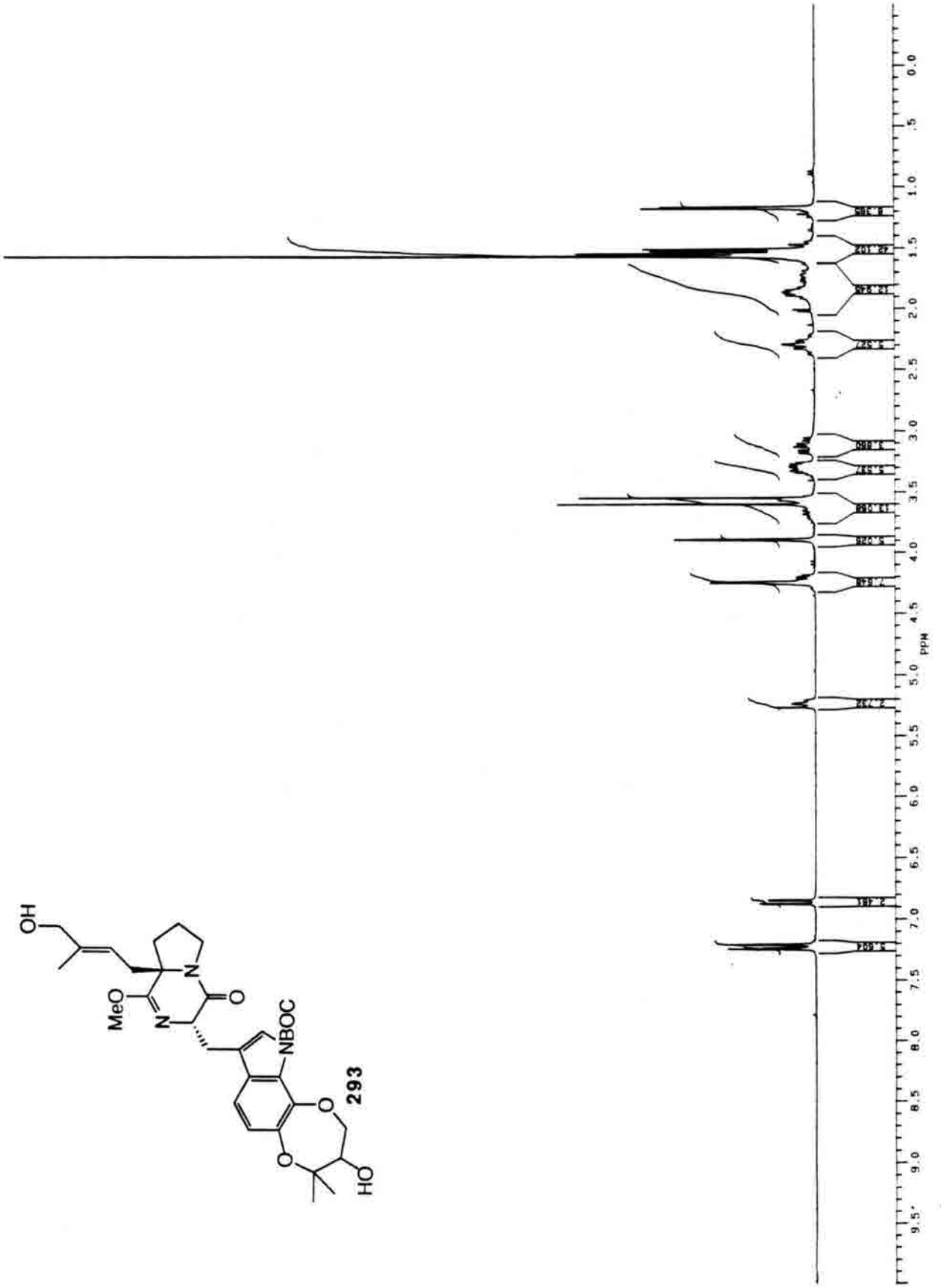
m); 4.18–4.23 (2H, m); 4.25 (4H, br s); 5.21–5.27 (2H, m); 6.857 (1H, d, J = 8.3Hz); 6.861 (1H, d, J = 8.3Hz); 7.22 (2H, d, J = 8.3Hz); 7.24 (2H, s).

IR (neat) 3401 (br), 2976, 1747, 1692, 1632, 1496, 1436, 1371, 1251, 1158, 733 cm^{-1}.

EI HRMS 597.3050 ($C_{32}H_{43}N_3O_8$ requires 597.3050).

m.p. 72–80 °C, foamy white solid.

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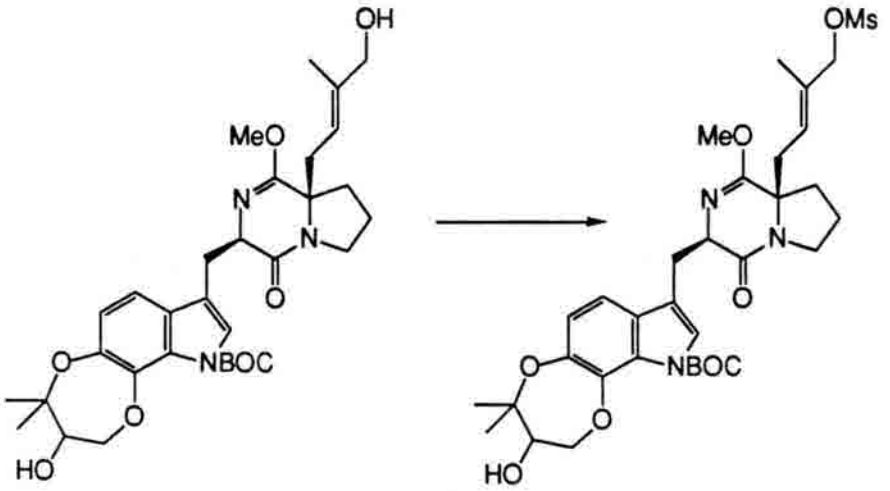
NBOC
O
O
HO
293
PPM



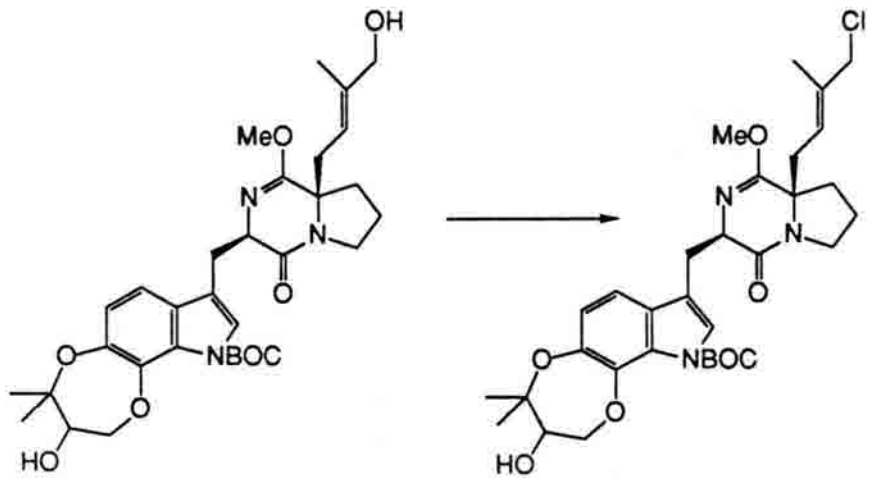
276 **288**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-[4-[methanesulfonyl)oxy]-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2H,10H-[1,4]dioxepino-[2,3-g]indole-10-carboxylate (288)

To a stirred solution of **276** (50.2mg, 0.076mmol, 1.0eq) in CH_2Cl_2 (0.8mL) under Ar at 0°C was added LiCl (13.0mg, 0.31mmol,4.0eq), DMAP (37.3mg, 0.31mmol, 4.0eq) and collidine (0.02mL, 0.15mmol, 2.0eq). Ten minutes later, MsCl (0.024mL,0.31mmol, 4.0eq) was added dropwise. The mixture was stirred overnight. The reaction was judged complete by TLC, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; radial, 1:2 hexanes/ethyl acetate. The product was a foamy solid. yield; 45.0mg, 87%.

^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1,40 (6H, S); 1.41 (3H, s); 1.57 (18H, s); 1.65 (6H, s); 1.78–2.22 (7H, m); 2.79–2.87 (2H, s); 3.13 (6H, s); 3.20–3.32 (2H, br m, D_2O exch.); 3.32 (2H, dd, J = 3.8, 14.5Hz); 3.617 (3H, s); 3.625 (3H, s); 3.92 (4H, s); 3.95–4.02 (2H, m); 4.30–4.46 (6H, m); 4.79–4.82 (2H, m); 5.27–5.32 (2H, m); 6.88 (2H, d, J = 8.3Hz); 7.161 (1H, d, J = 8.3Hz); 7.162 (1H, d, J = 8.3Hz); 7.39 (2H, s).

IR (neat) 2978, 1147, 1691, 1649, 1492, 1436, 1357, 1255, 1175, 1158, 966, 915, 728 cm^{-1}.



276 **289**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-(4-chloro-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2H,10H-[1,4]dioxepino-[2,3-g]-indole-10-carboxylate (289)

Dimethyl sulfide (0.67mL, 9.13mmol, 8.0eq) was added dropwise, to a stirred solution of NCS (1.22g, 9.13mmol, 8.0eq) in CH_2Cl_2 (51mL) at 0 °C under Ar. The resulting mixture was stirred for 10 minutes and then cooled (–23 °C). After 10 minutes **276** (682.4mg, 1.14mmol, 1.0eq) was added to the flask in one portion and the stirring continued for 6 hours. At this time the reaction flask was placed in a freezer (–35 °C) for 16 hours, followed by 10 additional hours of stirring at –23 °C. The mixture was then diluted with ethyl acetate washed with water, brine, dried over Na_2SO_4 and concentrated. chromatography; radial, 1:2 hexanes/ethyl acetate. yield; 565.8mg, 81%. {The yield of **289** was 2.12g (37% or 74% based on recovered **276**) with 5.60g of **276**}. An analytical sample was obtained by PTLC, 2:1 ethyl acetate/hexanes, (white foamy solid).

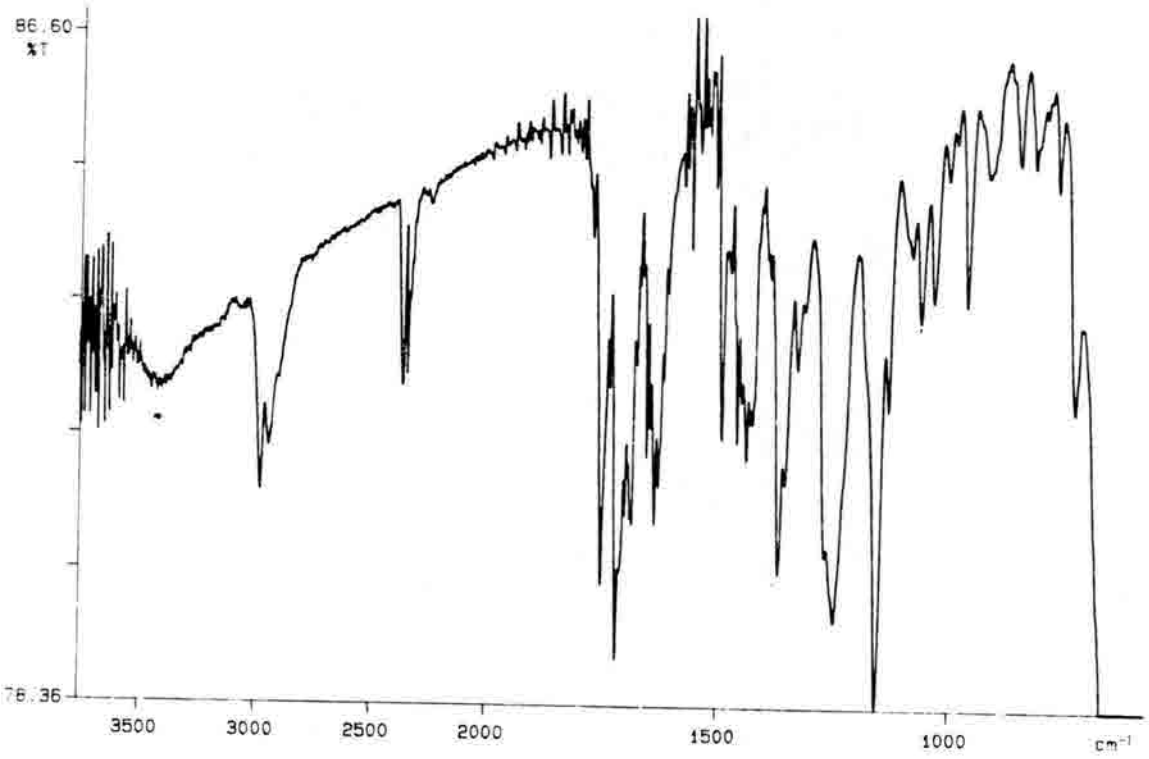
^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.17 (6H, S); 1.52 (6H, s); 1.57 (18H, s); 1.65 (6H, s); 1.73–2.20 (12H, s); 2.84 (2H, dd, J = 9.0, 14.4Hz); 3.06 (1H, br s, D_2O exch.); 3.10 (1H, br s, D_2O exch.); 3.26–3.36 (4H, m); 3.55–3.58 (4H,

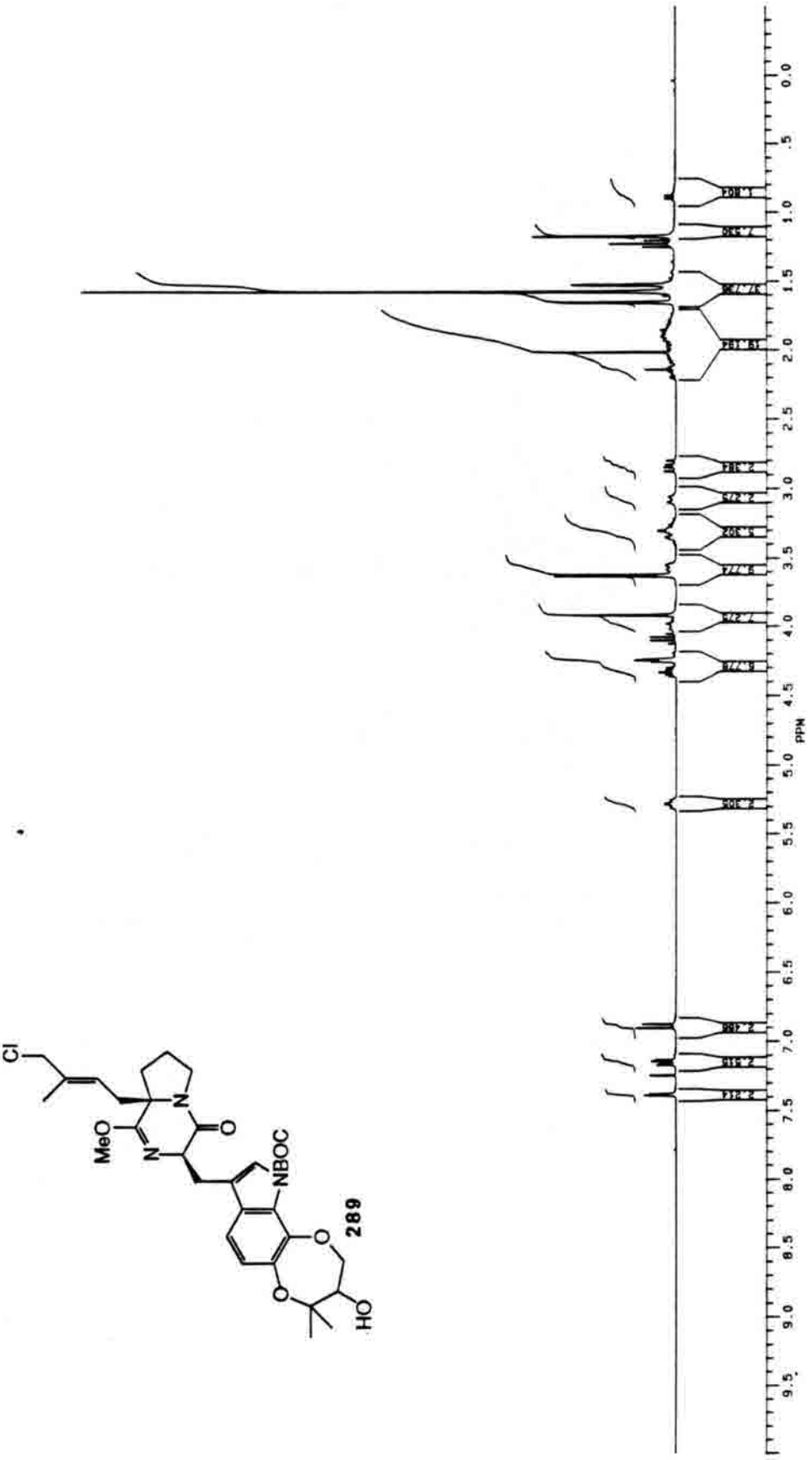
m); 3.62 (2H, s); 3.63 (2H, s); 3.91 (4H, s); 3.95–4.05 (2H, m); 4.24–4.25 (4H, m); 4.30–4.36 (2H, m); 5.28 (2H, m); 6.88 (2H, d, J = 8.3Hz); 7.14 (1H, d, J = 8.3Hz); 7.15 (1H, d, J = 8.3Hz); 7.376 (1H,s); 7.384 (1H, s).

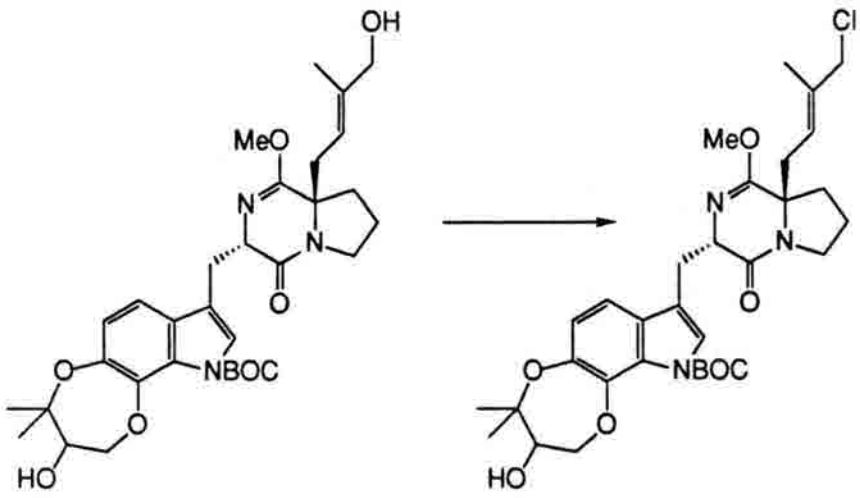
IR (neat) 3403, 2979, 1750, 1716, 1642, 1348, 1154 cm^{-1}.

EI HRMS 615.2709 ($C_{32}H_{42}N_3O_7Cl$ requires 615.2711).

microanalysis calc'd. for $C_{32}H_{42}N_3O_7Cl$: C, 62.38; H, 6.87; N, 6.82 found: C, 62.53; H, 6.86; N, 6.67.




Cl
MeO
N
N
O
NBOC
O
O
HO
289
PPM



293 **294**

[3α,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-(4-chloro-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2H,10H-[1,4]dioxepino-[2,3-g]-indole-10-carboxylate (294)

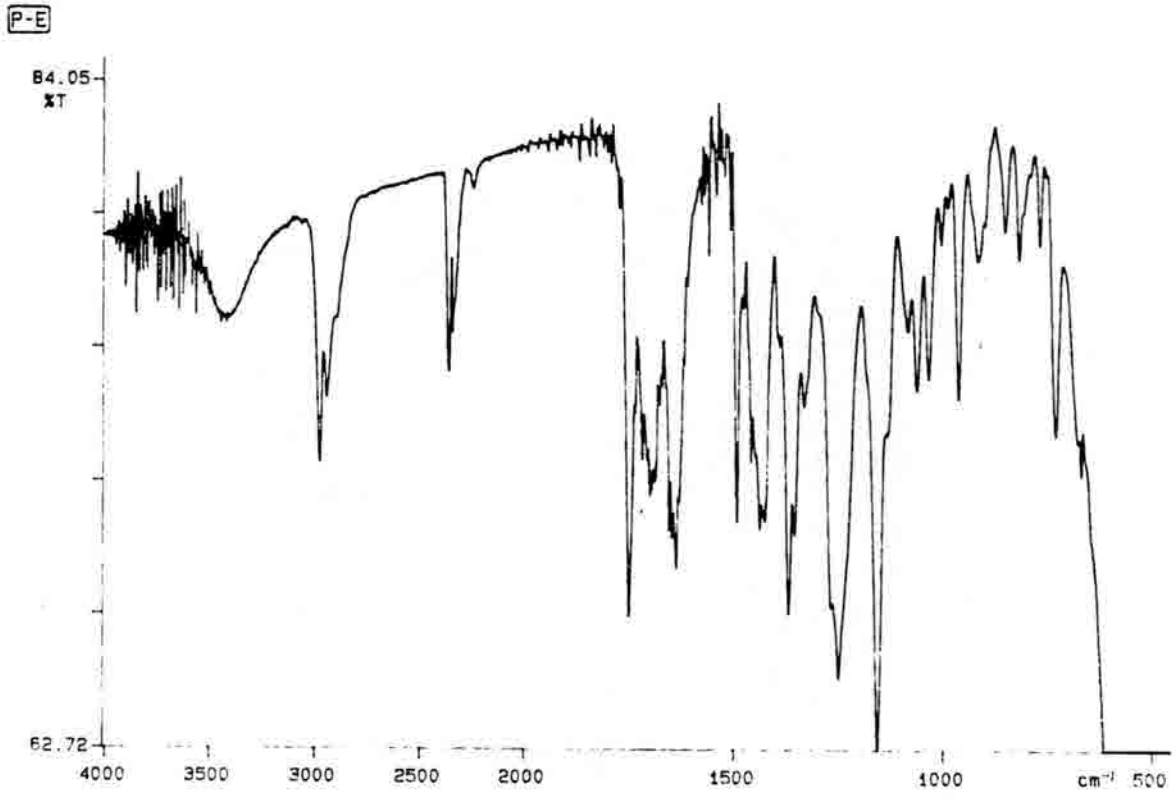
To a stirred solution of NCS (5.67g, 42.4mmol, 8.0eq) at 0 °C under Ar in CH_2Cl_2 (206mL) was added DMS (3.12mL, 42.4mmol, 8.0eq) dropwise. After 0.5 hours the mixture was cooled (–23 °C) and stirred an additional 0.5 hours. At this time the lactim ether-diol **293** (3.17g, 5.30mmol, 1.0eq) was added, (approximately 3g were added as a solid, the remaining was added as a solution in CH_2Cl_2 (30mL) via cannula). The white mixture was stirred for 12 hours, diluted with ethyl acetate washed with water, brine, dried over Na_2SO_4 and concentrated. chromatography; flash column 2:1 hexanes/ethyl acetate,1:1 hexanes/ethyl acetate. The product was obtained as a foamy glass. yield; 2.80g, 86%.

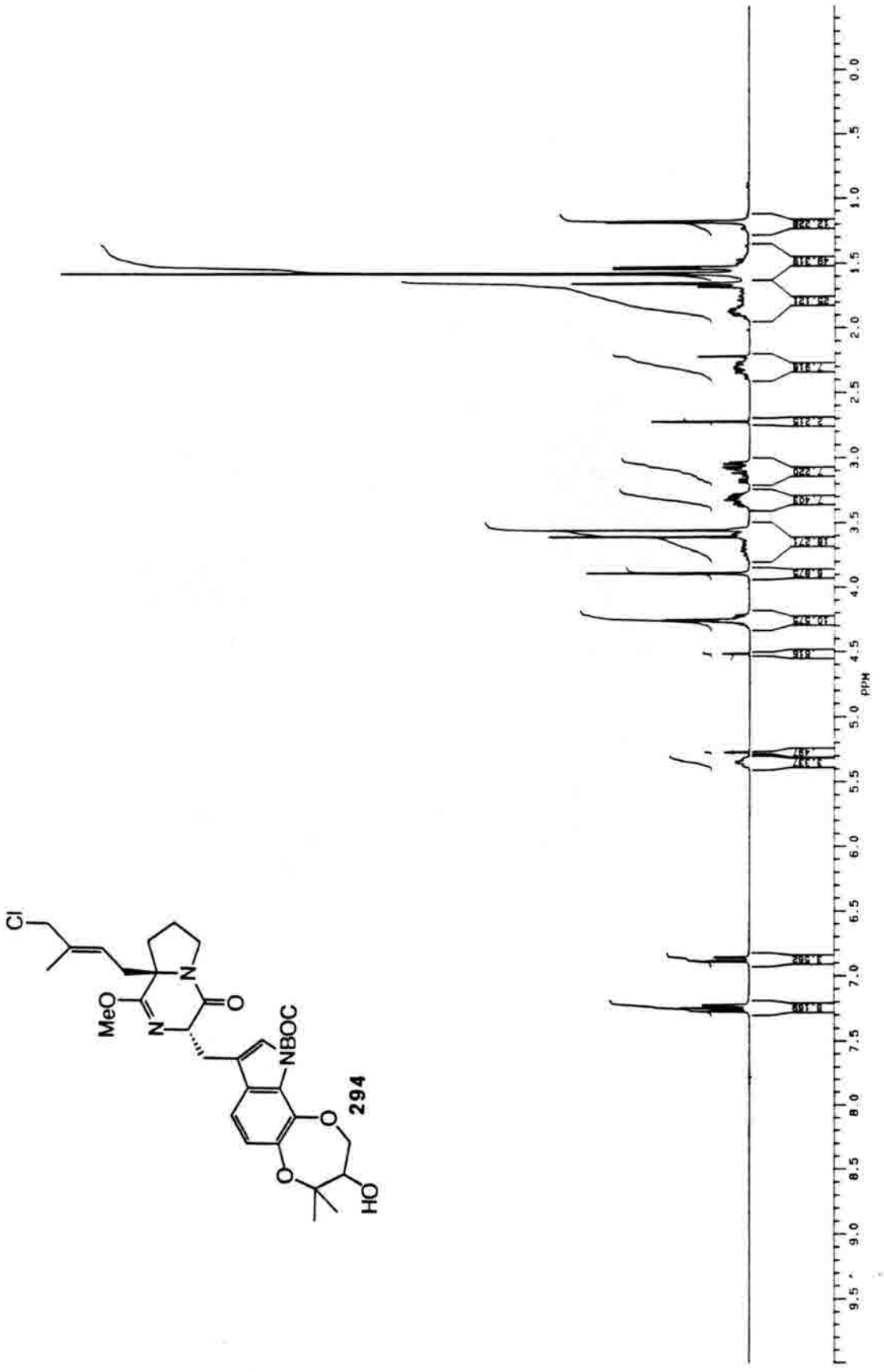
^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.17 (3H, s); 1.18 (3H, s); 1.52 (3H, s); 1.54 (3H, s); 1.57 (18H, s); 1.65 (6H, s); 1.71–1.92 (6H, m); 2.24–2.39 (4H, m); 3.03–3.19 (4H, m, 2H D_2O exch.); 3.28–3.37 (4H, m); 3.56 (3H, s); 3.60 (3H, s); 3.59–3.75 (4H, m); 3.89 (4H, s); 4.21–4.29 (6H, m); 5.35 (2H, t, J = 7.5Hz); 6.86

(1H, d, J = 8.3Hz); 6.87 (1H, d, J = 8.3Hz); 7.23 (2H, d, J = 8.3Hz); 7.22 (1H, s); 7.27 (1H, s).

IR (neat) 3412 (br), 2976, 1752, 1698, 1638, 1365, 1251, 1158 cm^{-1}.

EI HRMS 615.2714 ($C_{32}H_{42}N_3O_7Cl$ requires 615.2711)




Cl
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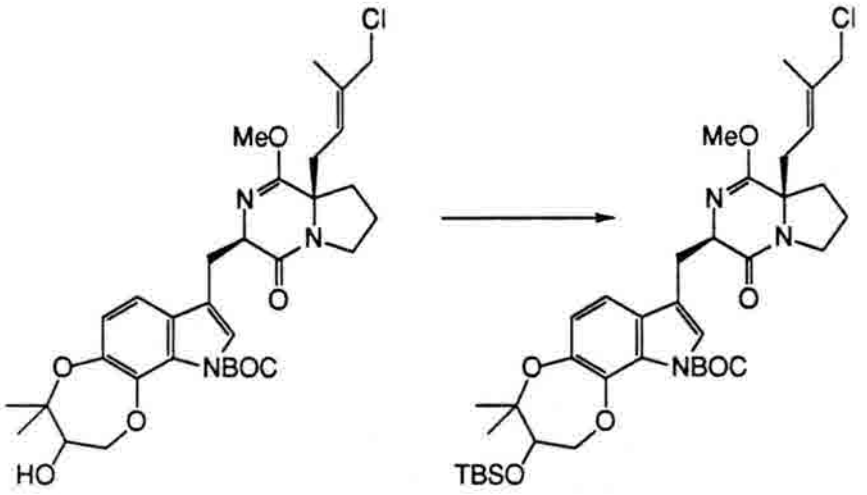
O
NBOC
O
O
HO
294
PPM



289 **290**

[3β,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-(4-chloro-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino-[2,3-g]-indole-10-carboxylate (290)

To a stirred solution of **289** (3.55g, 5.76mmol, 1.0eq) in CH_2Cl_2 (23mL) at 0 °C under Ar was added 2,6-lutidine (0.74mL, 6.34mmol, 1.1eq) followed by t-BDMOSTf (1.08mL, 6.34mmol, 1.1eq). After 3 hours an additional amount (1.1eq) of each reagent was added to the reaction flask, 2 hours later this was repeated. After one more hour, the mixture was diluted with ethyl acetate washed four times with water, once with brine, dried over Na_2SO_4 and concentrated. chromatography; column, yield; 3.23g, 77%. An analytical sample was obtained by PTLC, 1:1 hexanes/ethyl acetate to give a foamy white solid.

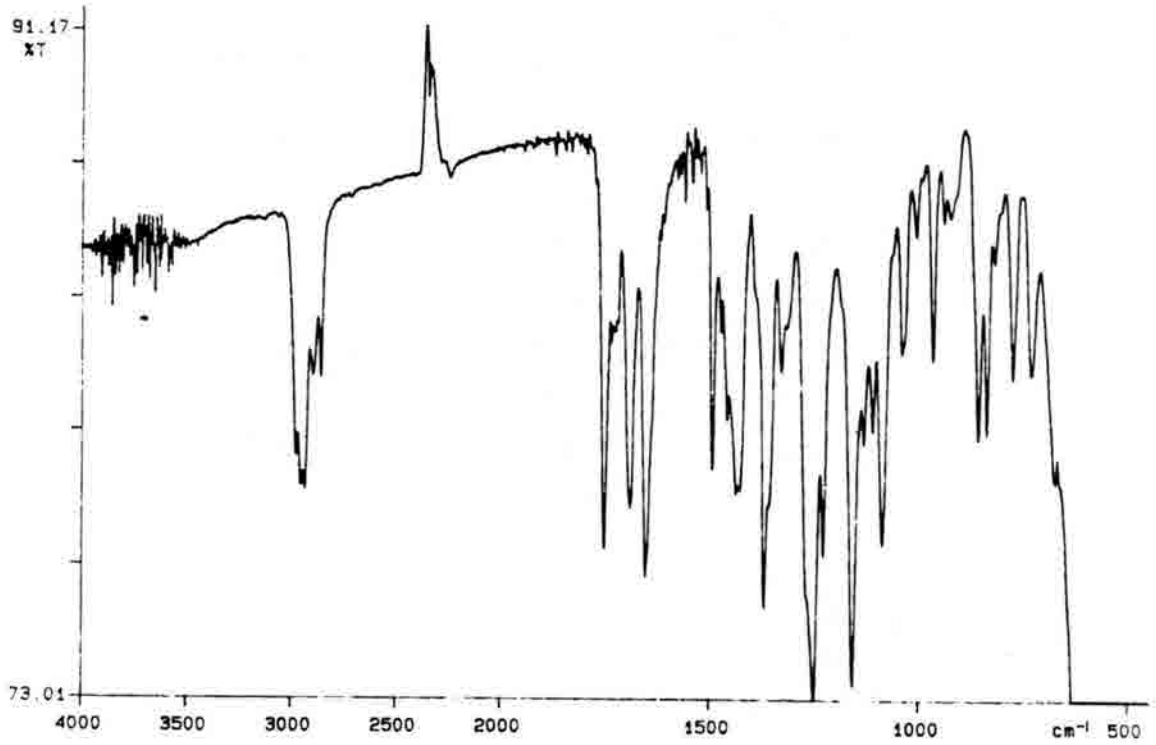
^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.12 (6H, s); 0.13 (6H, s); 0.88 (18H, s); 1.06 (6H, s); 1.47 (6H, s); 1.59 (18H, s); 1.65 (6H, s); 1.78–1.98 (8H, s); 2.02–2.12 (4H, m); 2.86 (2H, dd, J = 9.0, 14.6Hz); 3.31–3.34 (2H, m); 3.33 (2H, dd, J = 4.0, 13.6Hz); 3.62 (3H, s); 3.64 (3H, s); 3.71–3.79 (2H, m); 3.73 (1H, dd, J = 4.2, 9.8Hz); 3.77 (1H, dd, J = 4.4, 9.7Hz);

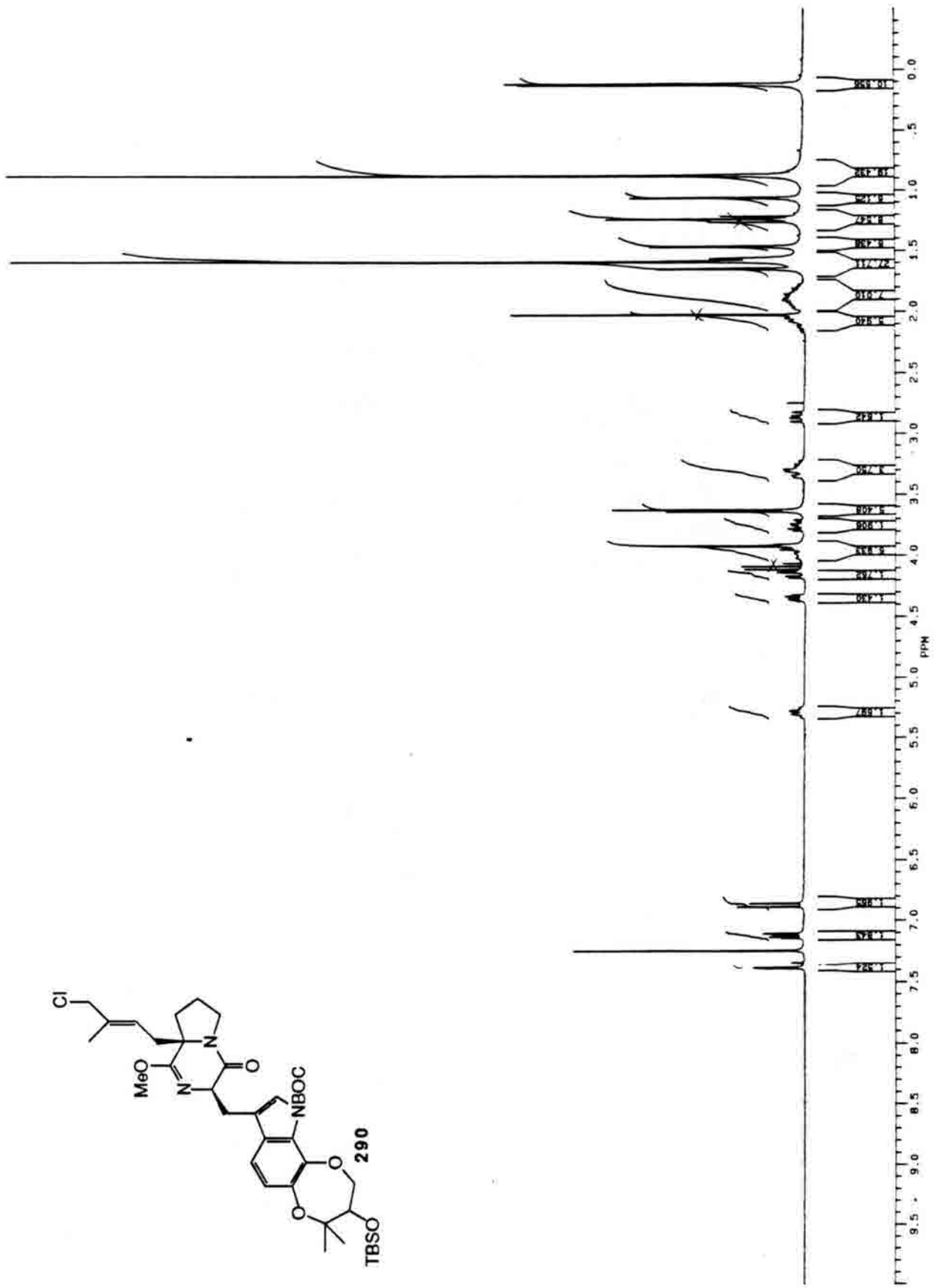
3.92 (4H, s); 3.94–4.01 (4H, m); 4.15 (2H, dd, J = 3.8, 12.4Hz); 4.32–4.37 (2H, m); 5.28–5.30 (2H, m); 6.87 (2H, d, J = 8.3Hz); 7.12 (2H, d, J = 8.3Hz); 7.13 (1H, d, J = 8.3Hz); 7.38 (2H, s).

IR (neat) 2930, 1750, 1691, 1652, 1494, 1424, 1366, 1248, 1159, 1088 cm^{-1}.

MS (EI) 729 *m/e* (rel intensity) 729 (M+, 4.2) 731 (M+2, 2.1) 629 (9.4) 361 (24.1) 360 (100) 167 (94.8) 57.2 (63).

microanalysis calc'd. for $C_{38}H_{56}N_3O_7SiCl$: C, 62.49; H, 7.73; N, 5.75 found: C, 62.57; H, 7.71, N, 5.55.

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O
NBOC
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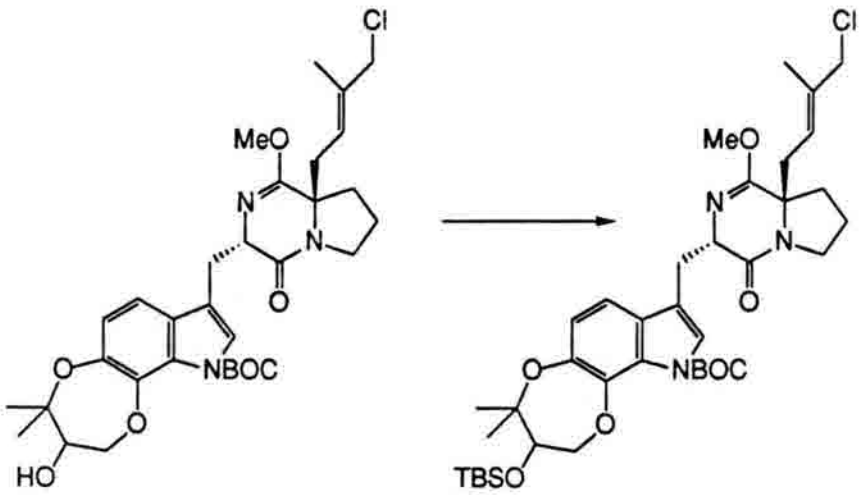
O
O
TBSO
290
PPM



294 **295**

[3α,8aβ(E)]-1,1-Dimethylethyl-8-[[3,4,6,7,8,8a-hexahydro-8a-(4-chloro-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino-[2,3-g]-indole-10-carboxylate (295)

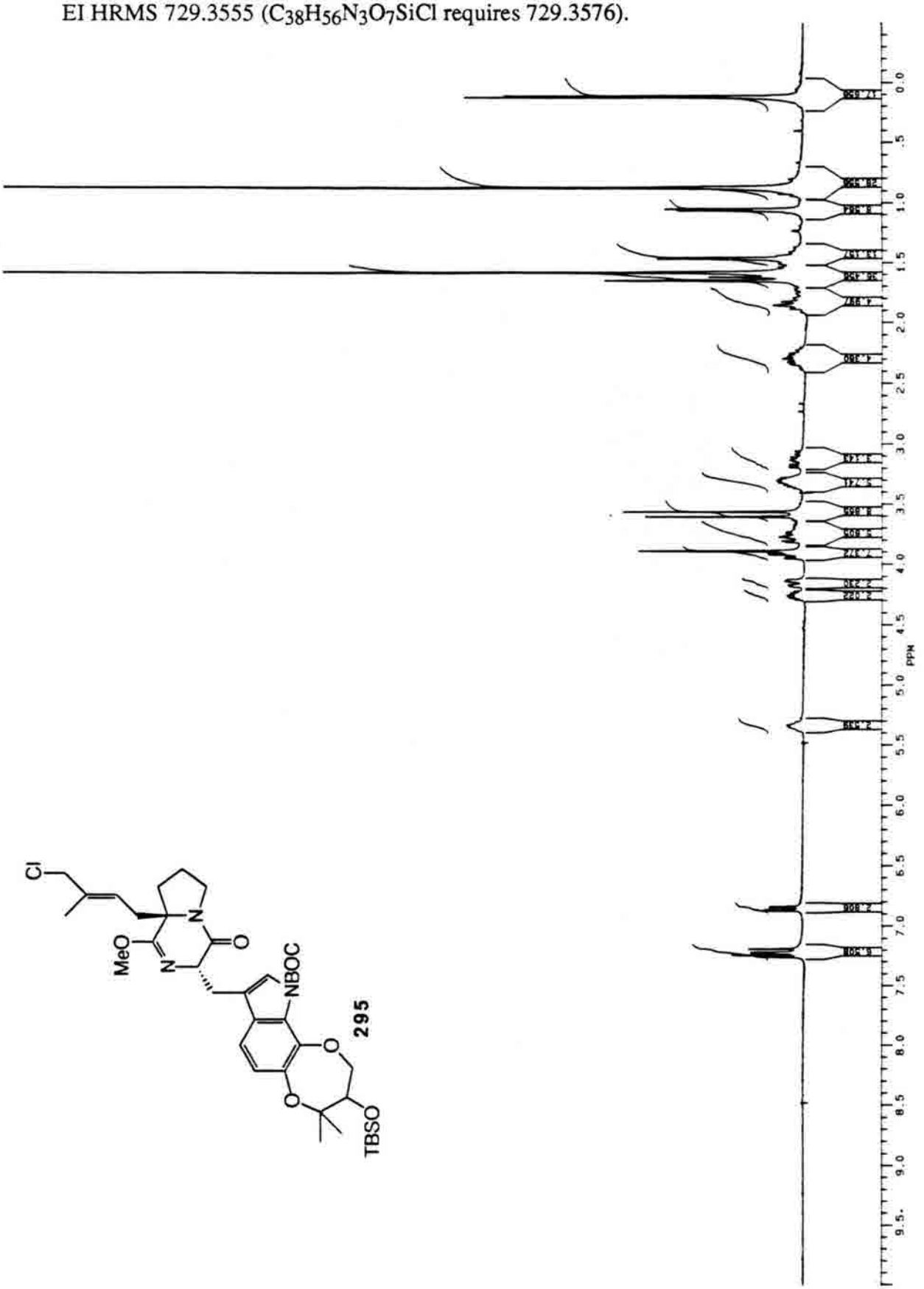
To a stirred solution of **294** (2.73g, 4.43mmol, 1.0eq) under Ar at 0 °C in CH_2Cl_2 (18mL) was added 2,6-lutidine (0.57mL, 4.87mmol, 1.1eq) followed by t-BDMSOTf (0.87mL, 4.87mmol, 1.1eq). After 1 hour the same amount (1.1eq) of each reagent was added and stirred 3 additional hours. The solution was diluted with ethyl acetate, washed with water, brine, dried over Na_2SO_4 and concentrated. chromatography; column, 1:2 ethyl acetate/hexanes. yield; 2.76g, 85%. An analytical sample was obtained by PTLC, 1:2 ethyl acetate/hexanes, (white foamy solid).

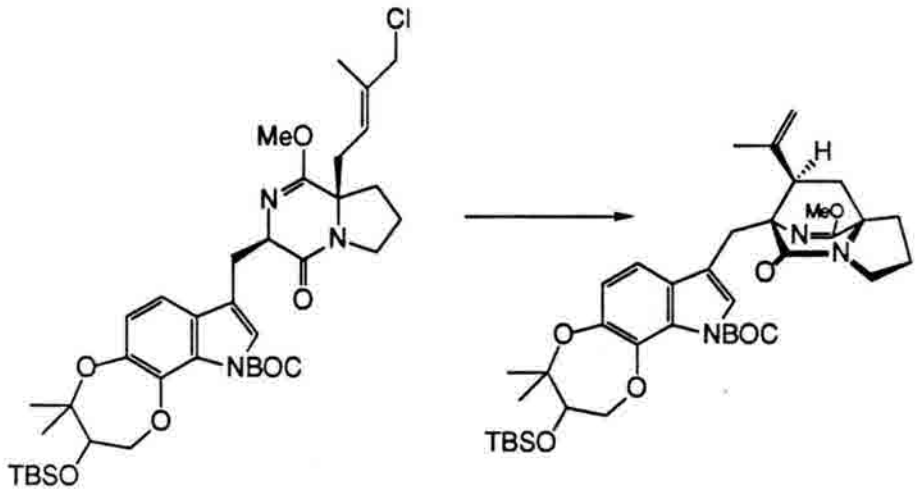
^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.12 (6H, s); 0.13 (6H, s); 0.87 (18H, s); 1.05 (3H, s); 1.06 (3H, s); 1.47 (6H, s); 1.50–1.53 (2H, m); 1.58 (18H, s); 1.65 (6H, s); 1.72–1.91 (4H, m); 2.21–2.37 (4H, m); 3.06–3.19 (2H, m); 3.28–3.36 (4H, m); 3.56 (3H, s); 3.60 (3H, s); 3.63–3.87 (4H, m): 3.89 (4H, s); 3.93 (2H, dd, J = 3.9, 9.8Hz); 4.13–4.18 (2H, m); 4.22–4.35 (2H, m); 5.30–5.40 (2H, m); 6.85 (1H, d, J = 8.3Hz); 6.86 (1H, d, J = 8.3Hz); 7.19–7.26 (4H, m).

IR (neat) 2949, 1751, 1693, 1652, 1493, 1424, 1369, 1250, 1156, 1086 cm^{-1}.

microanalysis calc'd. for $C_{38}H_{56}N_3O_7SiCl$: C, 62.49; H, 7.73; N, 5.75 found: C, 62.29; H, 7.61; N, 5.76.

EI HRMS 729.3555 ($C_{38}H_{56}N_3O_7SiCl$ requires 729.3576).

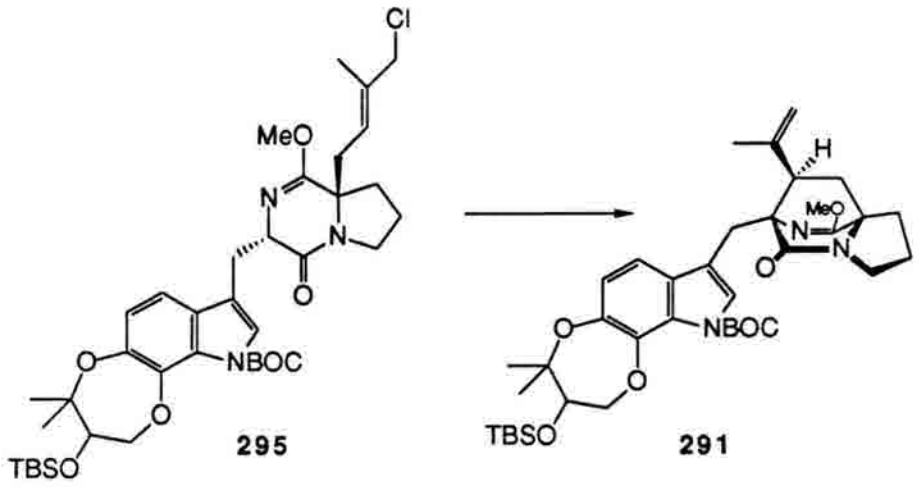




290 **291**

1,1-Dimethylethyl-8-[[7,8-dihydro-1-methoxy-10-(methylethenyl)-4-oxo-6H-3,8a-ethanpyrrolo[1,2-a]pyrazin-3(4*H*)-yl]]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino-[2,3-g]-indole-10-carboxylate (291)

To a stirred solution of **290** (1.43g, 1.96mmol, 1.0eq) in benzene (300mL) was added NaH (939mg, 39.16mmol, 20.0eq, freshly washed in pentane). This mixture was gently refluxed for 8.25 hours, diluted with ethyl acetate, washed with water and dilute HCl. The organic layer was isolated, washed with brine, dried over Na_2SO_4 and concentrated. chromatography; radial, 1:3 ethyl acetate/hexanes, yield; 1.26g, 93%. {The yield of **291** was 2.52g (86%) with 3.10g of **290**}



To a stirred solution of **295** (1.60g, 2.19mmol, 1.0eq) in benzene (313mL) was added NaH (1.05g, 43.8mmol, 20.0eq, freshly washed in pentane). This mixture was gently refluxed for 5.5 hours and stirred at room temperature overnight. At this time, a small sample was removed, washed with water and extracted with ethyl acetate. A crude $CDCl_3$ proton nmr indicated that the reaction was complete. The remaining mixture was diluted with ethyl acetate and washed with water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The two samples were combined. chromatography; radial, 1:3 ethyl acetate/hexaness yield; 1.29g, 85%. An analytical sample was obtained by PTLC, 1:3 ethyl acetate/hexanes, (white foamy solid).

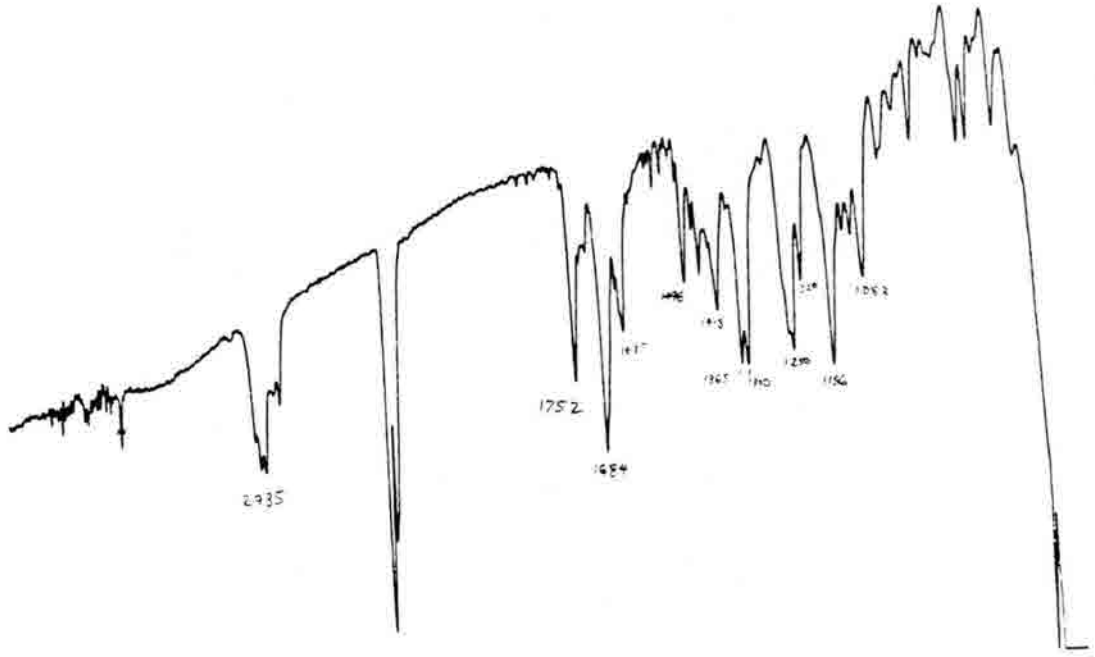
^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.12 (6H, s); 0.13 (6H, s); 0.872 (9H, s); 0.875 (9H, s); 1.46 (6H, s); 1.58 (18H, s); 1.61 (3H, s); 1.64 (3H, s); 1.72–2.03 (8H, m); 2.25–2.42 (2H, m); 2.47 (2H, dd, J = 5.1, 9.7Hz); 2.54 (2H, dd, J = 5.8, 9.7Hz); 3.05 (1H, ½ ABq, J = 15.0Hz); 3.07 (1H, ½ ABq, J = 15.0Hz); 3.31–3.53 (6H, m); 3.57 (3H, s); 3.64 (3H, s); 3.73–3.89 (2H, m); 3.94 (2H, dd, J = 3.7, 9.7Hz); 4.17 (2H, dd, J = 3.1, 11.6Hz); 4.62 (1H, s); 4.75 (1H, s); 4.78 (1H, s); 4.85 (1H, s); 6.82 (2H, d, J = 8.4Hz); 7.31 (1H, d, J = 8.4Hz); 7.38 (1H, d, J = 8.4Hz); 7.44 (1H, s); 7.52 (1H, s).

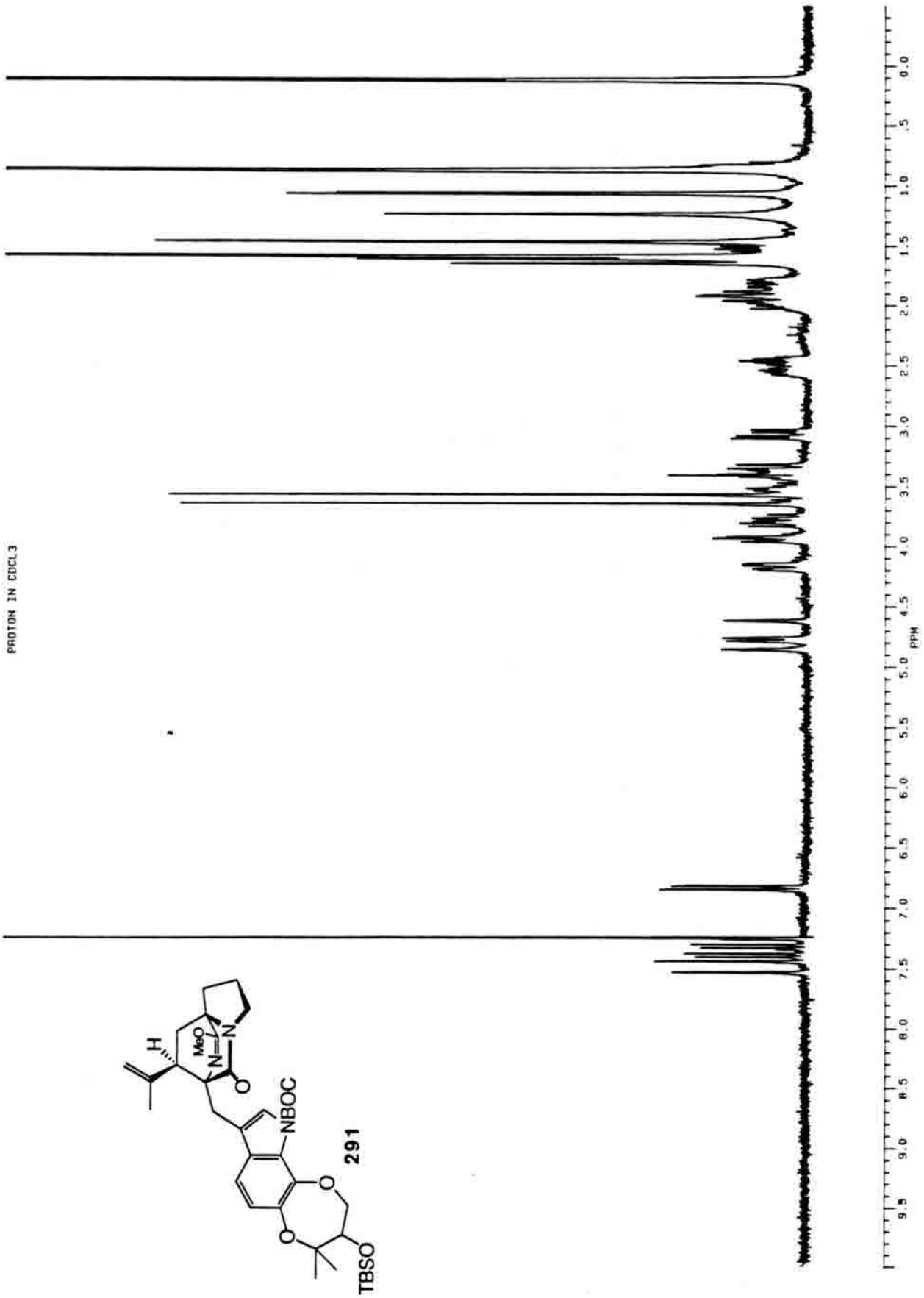
IR (neat) 2935, 1752, 1684, 1637, 1496, 1418, 1365, 1350, 1250, 1220, 1156, 1083 cm^{-1}.

EI HRMS m/e 693.3834 ($C_{38}H_{55}N_3O_7Si$ requires 693.3809).

microanalysis calc'd. for $C_{38}H_{55}N_3O_7Si$: C, 65.77; H, 7.99; N, 6.05 found: C, 65.85; H, 7.99; N, 5.91.

m.p.105–108 °C.

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3.0
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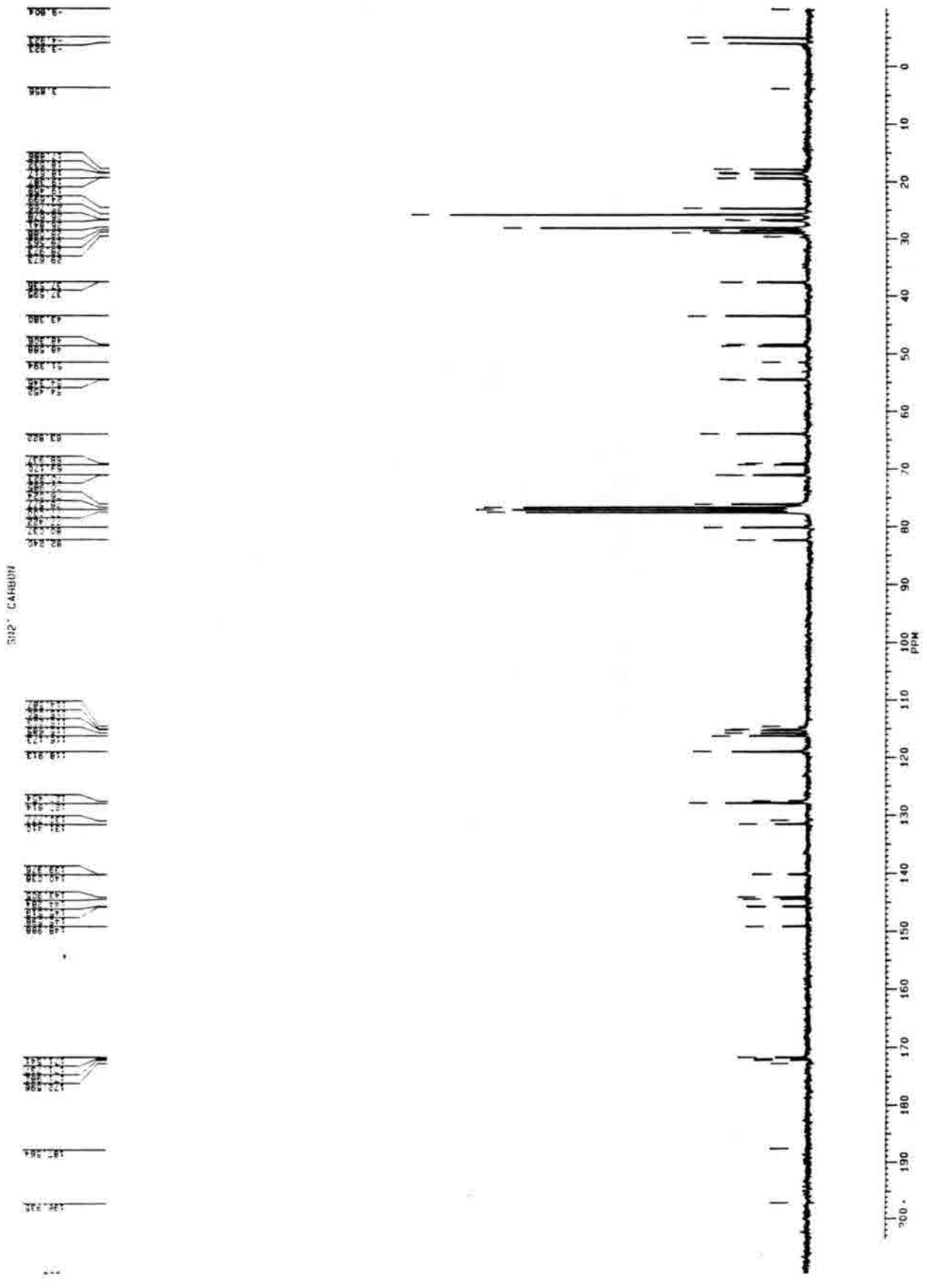
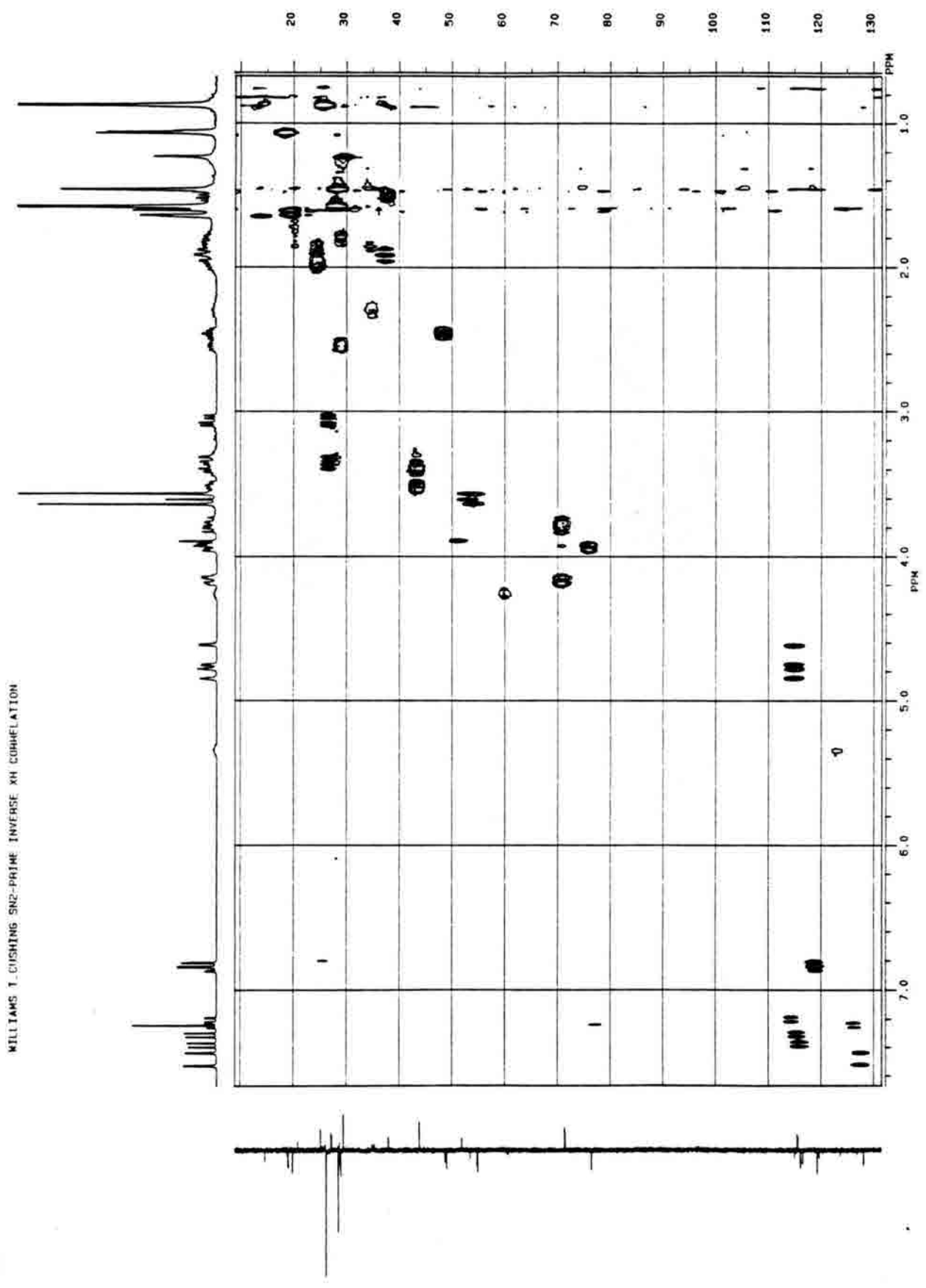
N
N
O
NBOC
O
O
TBSO
291


SN2' CARBON
PPM


WILLIAMS T.CUSHING SN2-PRIME INVERSE XH CORRELATION
20
30
40
50
60
70
80
90
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120
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PPM
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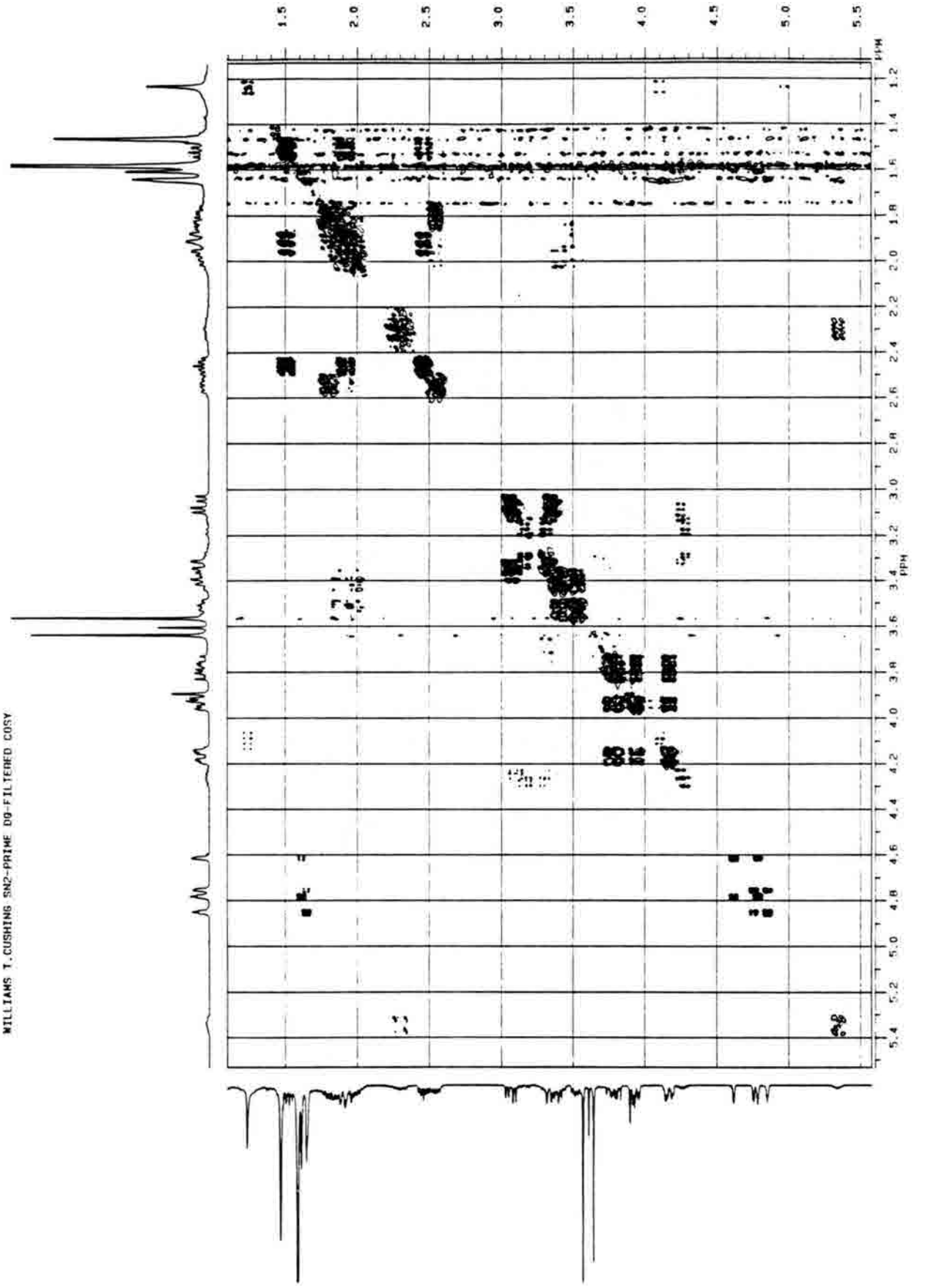
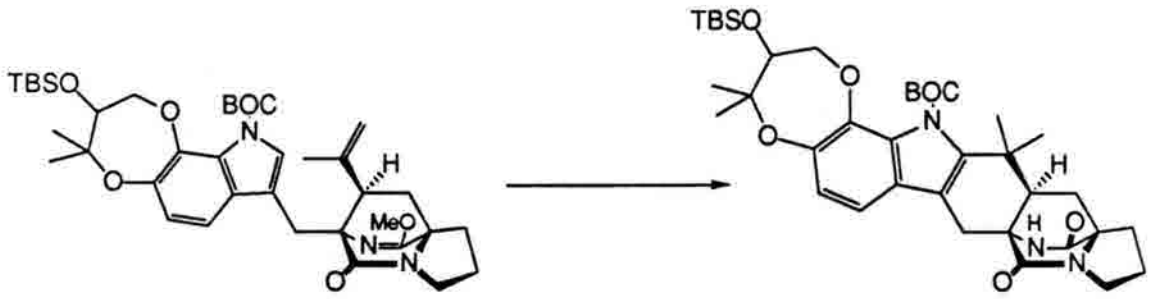
2.0
3.0
4.0
5.0
6.0
7.0
PPM


WILLIAMS T.CUSHING SN2-PRIME DQ-FILTERED COSY
PPM
PPM



291 **304**

1,1-Dimethylethyl-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-9,17-dioxo-11*H*,16*H*-8a,13a-(Iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylate (304)

To a flask charged with $PdCl_2$ (827.9mg, 4.67mmol, 3.0eq) and $AgBF_4$ (605.3mg, 3.11mmol, 2.0eq) was added dry CH_3CN (50mL). This was stirred for 6.5 hours, when a solution of **291** (1.08g, 1.56mmol, 1.0eq) in CH_3CN (5.0mL) was syringed into the flask. After 48 hours EtOH (55mL) was added, followed by small portions of $NaBH_4$ (590mg, 15.6mmol, 10.0eq) at 0 °C. The addition was complete in 0.5 hours and the mixture allowed to stir an additional 0.5 hours. The black mixture was filtered to remove palladium and the solvent evaporated. The residue was dissolved in ethyl acetate, washed with dilute (0.01M HCl), brine, dried over Na_2SO_4 and concentrated. chromatography; radial, 25:25:1 CH_2Cl_2/Et_2O/MeOH. The product was obtained as a white crystalline solid. yield; 676.3mg, 63%. An analytical sample was obtained by PTLC, 25:25:1 CH_2Cl_2/Et_2O/MeOH, (white crystalline solid).

^{1}NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.081 (6H,s); 0.11 (6H, s); 0.87 (9H, s); 0.88 (9H, s); 1.08 (3H, s); 1.17 (3H, s); 1.26 (3H, s); 1.27 (3H, s); 1.34 (3H, s); 1.35 (3H, s); 1.44 (3H, s); 1.46 (3H, s); 1.56 (9H, s); 1.58 (9H, s); 1.81–1.90 (2H, m); 1.96–2.06 (6H, m); 2.20 (2H, dd, J = 10.3, 13.5Hz); 2.52–2.60 (4H, m); 2.78 (2H, dt, J = 6.5, 12.9Hz); 3.36–3.49 (2H, m); 3.51–3.57 (2H, m); 3.51–3.57 (2H, m); 3.63–3.84 (4H, m); 3.88–3.92 (2H, m); 4.04–4.16 (2H, m); 6.24 (1H, s, D_2O exch.);

6.26 (1H, s, D_2O exch.) 6.78 (1H, d, J = 8.3Hz); 6.80 (1H, d, J = 8.5Hz); 6.98 (1H, d, J = 8.2Hz); 6.99 (1H, d, J = 8.4Hz).

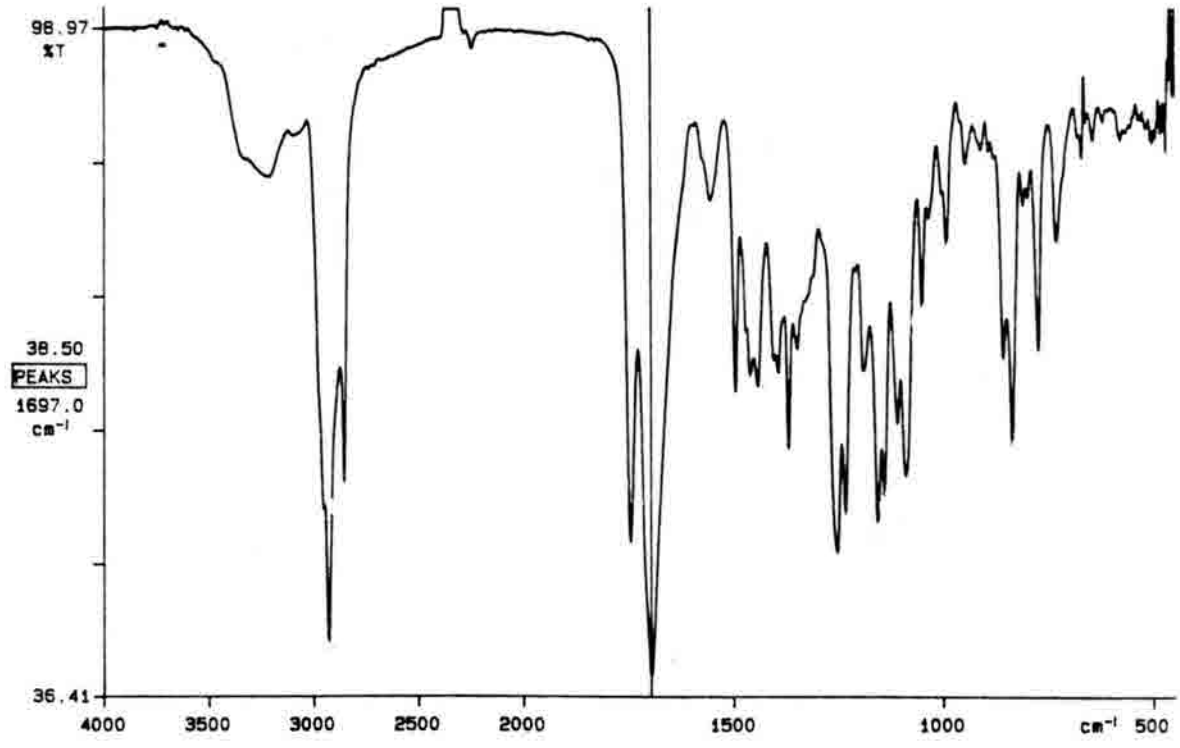
^{13}C NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ –5.2, –5.1, –5.0, –4.5, –4.3, 17.6. 18.7, 19.3, 19.7, 19.9, 24.3,.25.5, 25.6, 26.9, 26.2, 27.2, 27.8, 27.9, 28.3, 28.5, 29.1, 31.1, 36.2, 43.8, 50.5, 50.6, 53.3, 54.8, 55.7, 59.4, 60.16, 60.22, 66.3, 67.6, 71.1, 72.7, 75.9, 78.0, 80.5, 84.1, 84.3, 108.3, 112.4, 112.5, 113.6, 117.9, 118.5, 124.6, 124.9, 128.7, 128.9, 129.4, 137.7, 138.3, 139.4, 139.6, 143.0, 143.2, 152.9, 153.0, 168.3, 174.1.

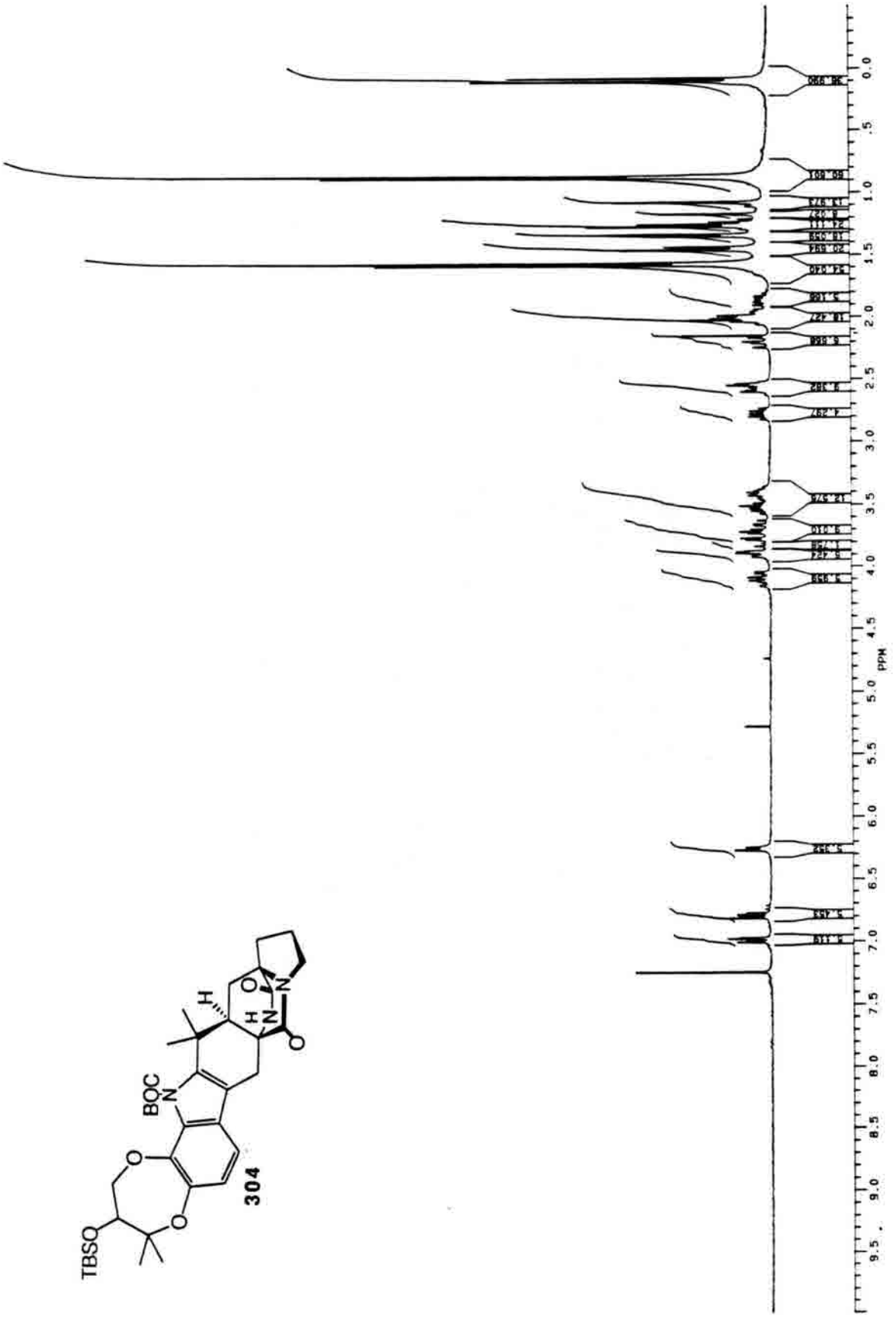
IR (neat) 3214, 2928, 2856, 1745, 1556, 1496, 1443, 1368, 1252, 1233, 1154, 1141, 1091, 1052, 994, 859, 838, 777, 733.

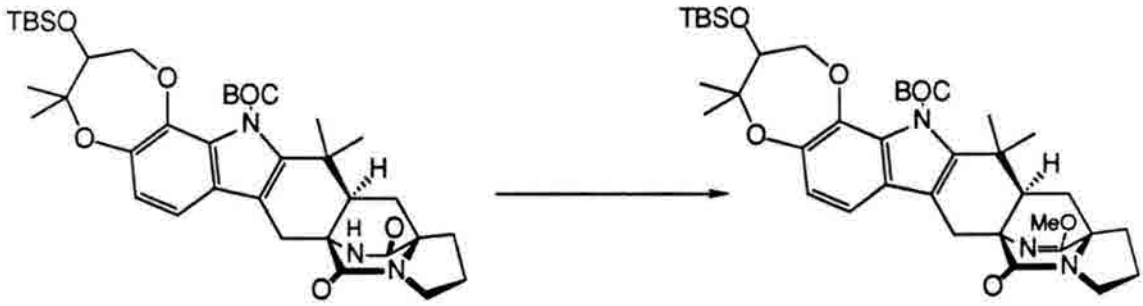
microanalysis calc'd. for $C_{37}H_{53}N_3O_7Si$: C, 65.36; H, 7.86; N, 6.18 found: C, 65.18; H, 7.77; N, 6.18.

MS (EI) 679 *m/e* (rel intensity) 679 (M^+, 0.3) 580 (20.4) 579 (51) 73 (100).

EI HRMS m/e 679.3661 ($C_{37}H_{53}N_3O_7Si$ requires 679.3653).




TBSO
BOC
304
PPM



304 **306**

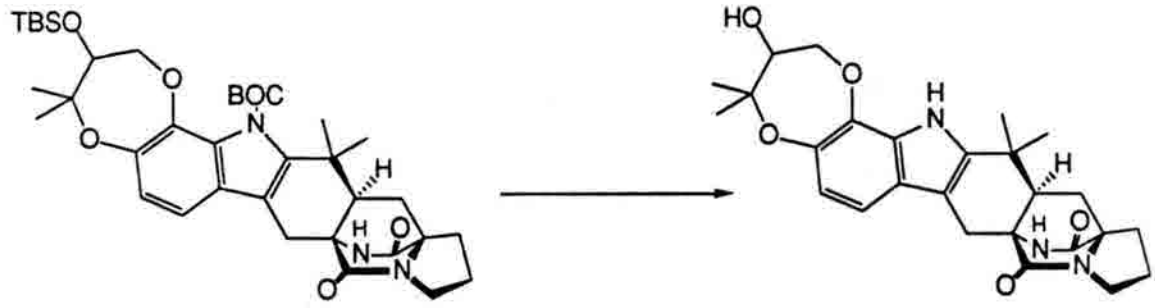
1,1-Dimethylethyl-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-17-methoxy-9-oxo-11H,16*H*,8a,13a-(Iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-a]indolizino [6,7-h]carbazole-16-carboxylate (306)

To a stirred solution of **304** (26.1mg, 0.38mmol, 1.0eq) in CH_2Cl_2 (1mL) under Ar, at 0 °C was added Na_2CO_3 (81.0mg, 0.764mmol, 20.0eq). After 10 minutes Me_3OBF_4 (28.3mg, 0.191mmol, 5.0eq) was added in one portion. The mixture was stirred for 4.0 hours at room temperature, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; PTLC, 1:2 hexanes/ethyl acetate. The product is a white crystalline solid. yield; 19.6mg, 74%.

^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ TMS 0.10–0.15 (12H, M); 0.89 (9H, s); 0.90 (9H, s); 1.09 (6H, s); 1.26 (3H, s); 1.29 (3H, s); 1.33 (3H, s); 1.36 (3H, s); 1.46 (3H, s); 1.48 (3H, s); 1.58 (9H, s); 1.60 (9H, s); 1.76–2.51 (10H, m); 2.23–2.31 (2H, m); 2.60–2.70 (2H, m); 3.027 (1H, ½ ABq, J = 16.4Hz); 3.032 (1H, ½ ABq, J = 16.4Hz); 3.31–3.41 (2H, m); 3.46–3.54 (2H, m); 3.68 (2H, dd, J = 9.1, 12.1Hz); 3.90 (2H, ½ ABq, J = 16.3Hz); 4.08 (2H, dd, J = 3.5, 11.9Hz); 3.87–3.94 (2H, m); 6.79 (1H, d, J = 8.3Hz); 6.80 (1H, d, J = 8.3Hz); 7.063 (1H, d, J = 8.3Hz); 7.061 (1H, d, J = 8.3Hz).

IR (neat) 2952, 2886, 1745, 1683, 1640, 1496, 1412, 1355, 1252, 1232, 1156, 1140, 1111, 1090, 1052, 992, 838, 770.cm^{-1}.

EI HRMS m/e 693.3810 ($C_{38}H_{55}N_3O_7Si$ requires 693.3810).



304 **312**

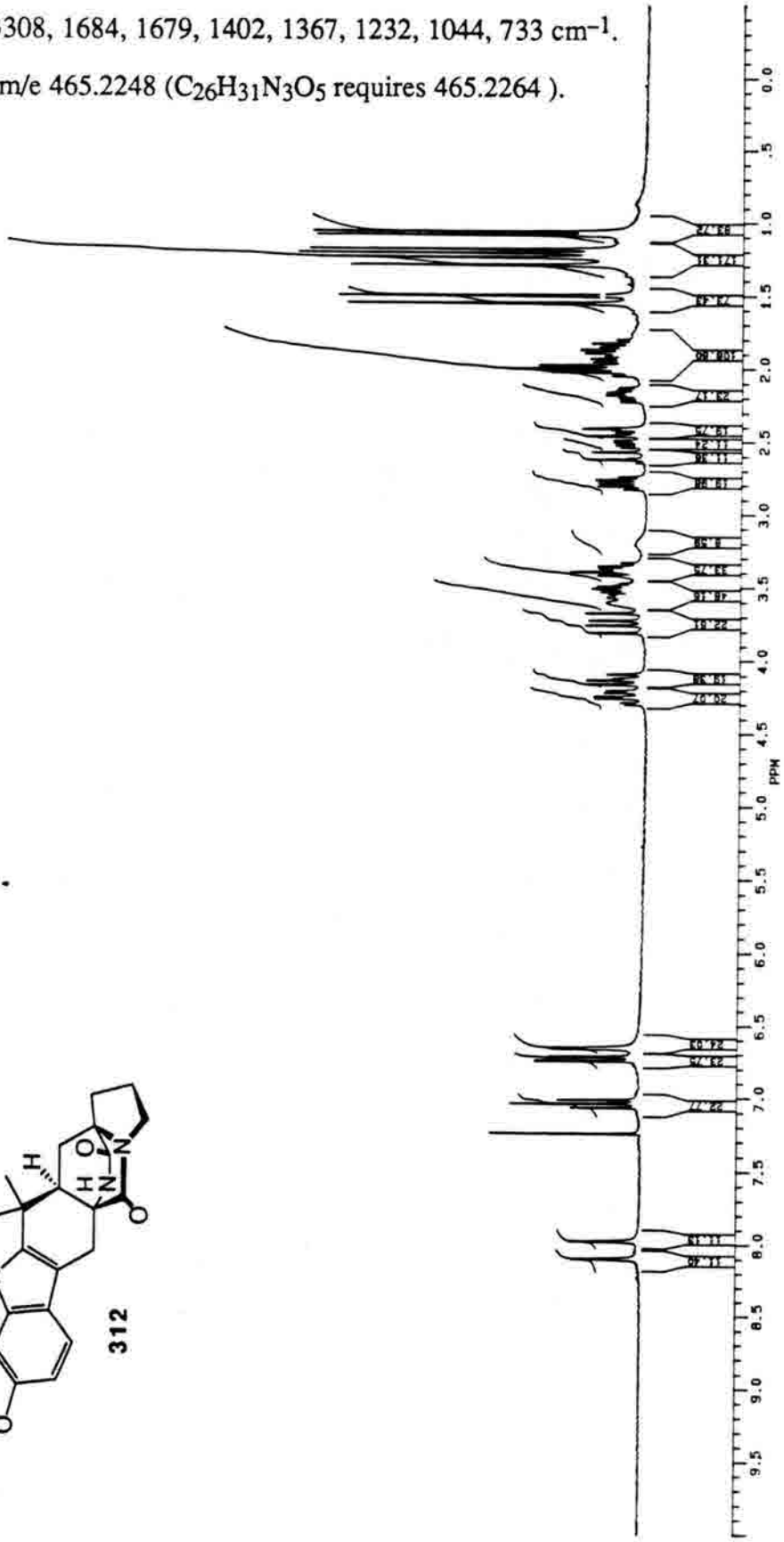
3-[Hydroxy]-3,4,8,12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-9,17-dioxo-11*H*,16*H*-8a,13a-(Iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole (306)

To a stirred solution of **304** (150mg, 0.220mmol, 1.0eq) in CH_2Cl_2 (4.4mL) under N_2 at 0 °C was added TFA (1.4mL, 17.8mmol, 80eq) dropwise. The reaction was allowed to reach room temperature overnight. The solution was concentrated, and the residue taken up in ethyl acetate. The resulting solution was washed with 10% Na_2CO_3 and brine. The organic layer was dried over Na_2SO_4 and concentrated to dryness. chromatography; radial, ethyl acetate. yield; 102mg, 95%. An analytical sample was obtained by PTLC, 1:1 ethyl acetate/hexanes, (white crystalline solid).

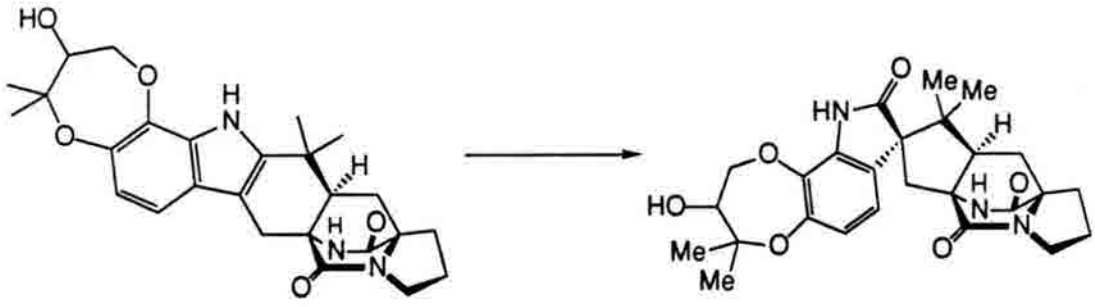
^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.06 (3H, s); 1.08 (3H, s); 1.18 (3H, s); 1.20 (1.23 (3H, s); 1.29 (3H, s); 1.49 (3H, s); 1.55 (3H, s); 1.79–2.04 (8H, m); 2.17 (2H, td, J = 5.1, 11.9Hz); 2.43 (1H, m); 2.43 (1H, ½ ABq, J = 15.5Hz); 2.51 (1H, dd, J = 4.8, 10.2Hz); 2.59 (1H, ½ ABq, J = 15.5Hz); 2.78 (2H, dt, J = 6.5, 12.9Hz); 3.21 (1H, br s, D_2O exch.) 3.33–3.90 (4H, m); 3.41–3.56 (4H, m); 3.60 (1H, br s, D_2O exch.); 3.70 (1H, ½ ABq, J = 15.4Hz); 3.78 (1H, ½ ABq, J = 15.4Hz); 4.12 (2H, dd, J = 8.4, 12.0Hz); 4.25 (2H, td, J = 4.0, 12.2Hz); 6.65 (2H, s, D_2O exch.); 6.72 (1H, d, J = 8.3Hz); 6.73 (1H, d, J = 8.3Hz); 7.02 (1H, d, J = 7.9Hz); 7.05 (1H, d, J = 8.1Hz); 7.98 (1H, s, D_2O exch.); 8.10 (1H, s, D_2O exch.).

IR (neat) 3308, 1684, 1679, 1402, 1367, 1232, 1044, 733 cm^{-1}.

EI HRMS m/e 465.2248 ($C_{26}H_{31}N_3O_5$ requires 465.2264).



312



312 **315**

14-Deoxy-24,29-demethyl-25-dihydro-25-hydroxy-12-oxo-17-Norparaherquamide (315)

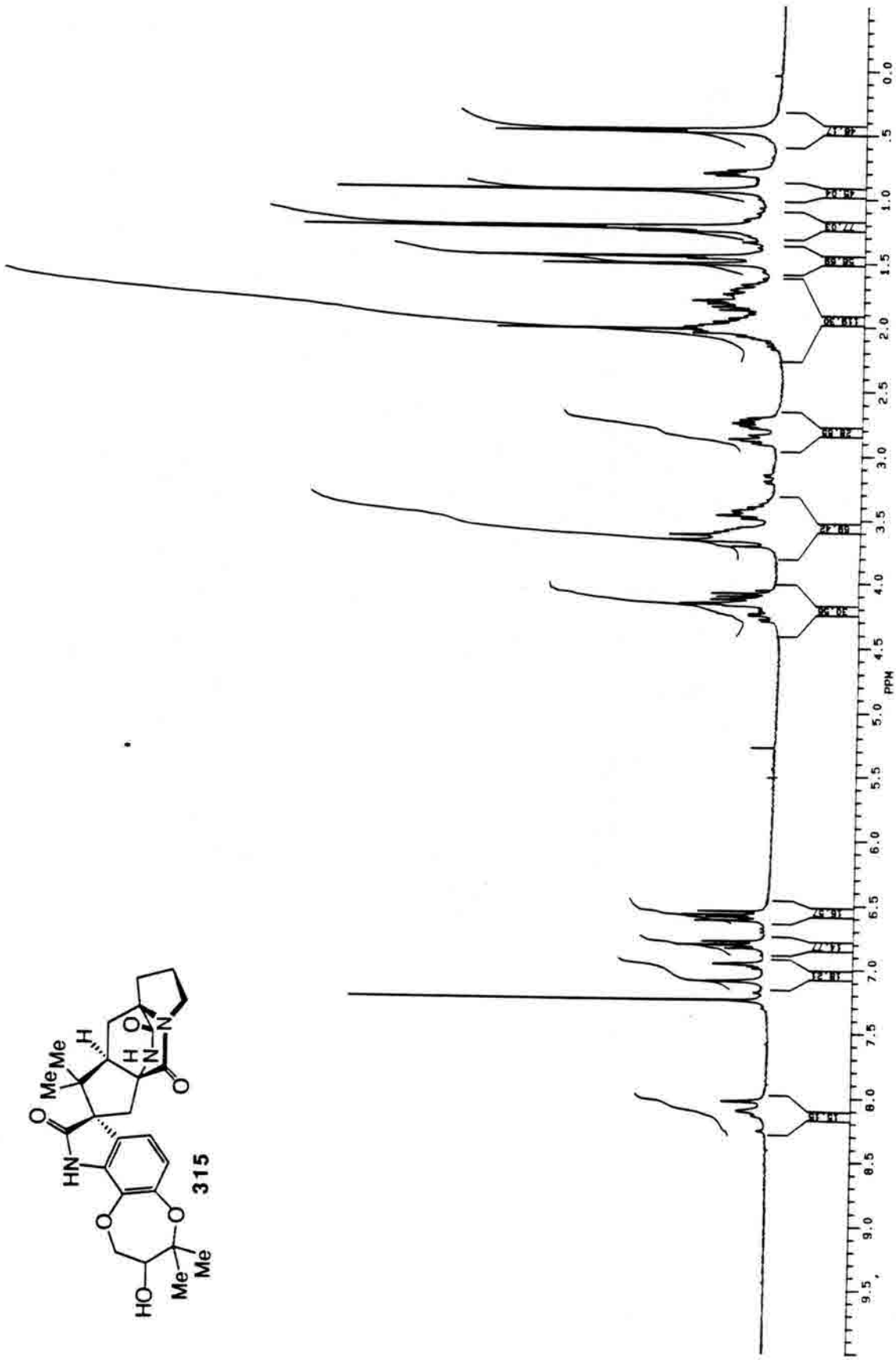
To a stirred mixture of **312** (16.5mg, 0.0354mmol, 1.0eq) in CH_2Cl_2 (0.7mL) at 0 °C under N_2 was added Et_3N (4.6uL, 0.039mmol, 1.1eq) followed by t-BuOCl (5.4uL, 0.039mmol, 1.1eq). After 0.5 hours, the resulting yellow clear solution was concentrated to dryness (keeping the flask cold). The residue was immediately subjected to a solution of MeOH/H_2O/AcOH (40:20:1) and stirred under N_2 at room temperature for 0.5 hours. The solution was diluted with saturated $NaHCO_3$, and the organic layer washed three times with sat.$NaHCO_3$, brine, dried over Na_2SO_4, and concentrated to dryness. chromatography; PTLC, 20:1 CH_2Cl_2/MeOH. The product was obtained as an amorphous solid. yield, 5.0mg, 29%.

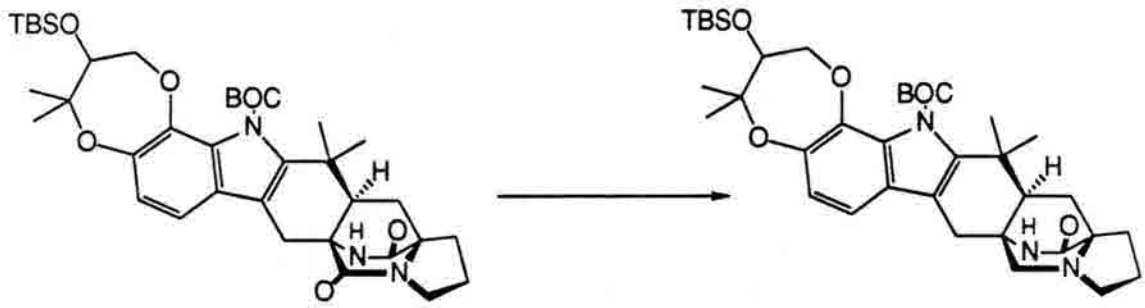
1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.46 (3H, s); 0.48 (3H, s); 0.93 (6H, s); 1.22 (3H, s); 1.23 (3H, s); 1.45 (3H, s); 1.51 (3H, s); 1.65–2.09 (14H, m); 2.71–2.79 (2H, m); 2.87 (2H, td, J = 3.2, 9.3Hz); 3.40–4.99 (2H, m); 3.56–3.66 (6H, m, 2H D_2O exch.); 4.08–4.26 (4H, m); 6.56 (1H, d, J = 8.1Hz); 6.61 (1H, d, J = 8.1Hz); 6.80 (1H, d, J = 7.7Hz); 6.82 (1H, d, J = 7.8Hz); 6.96 (1H, s, D_2O exch.); 7.09 (1H, s, D_2O exch.); 8.03 (1H, s, D_2O exch.); 8.11 (1H, s, D_2O exch.).

IR (neat) 3411, 3237, 1698, 1632, 1496, 1404, 1333, 1213, 728 cm^{-1}.

MS (EI) 481 *m/e* (rel intensity) 481 (M^+, 23.9) 412 (15.2) 249 (12.7) 220 (100) 149 (60.6).

EI HRMS m/e 481.2194 ($C_{26}H_{31}N_3O_6$ requires 481.2213).


315
PPM



304 **309**

1,1-Dimethylethyl-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15,15-octahydro-4,4,15,15-tetramethyl-17-oxo-11H,16H,8a,13a-(Iminomethano)-2H,9H-[1,4]dioxepino[2,3-a]indolizino [6,7-h]carbazole-16-carboxylate (309)

To a stirred solution of **304** (164mg, 0.240mmol, 1.0eq) in THF (4.9mL) at –78 °C under Ar was added Et_3Al (0.14mL, 0.264mmol, 1.1eq, 1.9M) dropwise. After 10 minutes the solution was warmed to 0 °C and AlH_3·DMEA (6.0mL, 1.20mmol, 5.0eq, 0.2M in toluene) added dropwise. The ice bath was removed and the solution stirred for 1h 20 min at room temperature. At this time MeOH (4.7mL) and AcOH (0.31mL) were syringed into the flask, followed by $NaCNBH_3$ (179mg, 2.85mmol, 11.9eq). This mixture was stirred for 10 minutes, and then the solvent removed and replaced with ethyl acetate. The resulting solution was washed with $NaHCO_3$ (sat.), brine and dried over Na_2SO_4. chromatography; radial, 1:1 hexanes/ethyl acetate. yield, 102mg, 64%. An analytical sample was obtained by PTLC, 1:1 ethyl acetate/hexanes, (white crystalline solid).

^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.085 (6H, s); 0.11 (6H, s); 0.87 ((H, s); 0.88 (9H, s); 1.12 (3H, s); 1.15 (3H, s); 1.23 (3H, s); 1.24 (3H, s); 1.36 (3H, s); 1.37 (3H, s); 1.45 (6H, s); 1.59 (9H, s); 1.61 (9H, s); 1.88–1.92 (3H, s); 1.97–2.10 (2H, m); 2.17–2.26 (2H, m); 2.54–2.63 (2H, m); 2.70 (2H, ½ ABq, J = 15.5Hz); 2.829 (1H, ½ ABq, J =15.4Hz); 2.835 (1H, ½ ABq, J = 15.6Hz); 3.06–3.09 (2H, m); 3.45–3.49 (2H, m); 3.67–3.85 (4H, m); 3.90 (2H, dd, J = 3.4, 8.7Hz); 4.09–

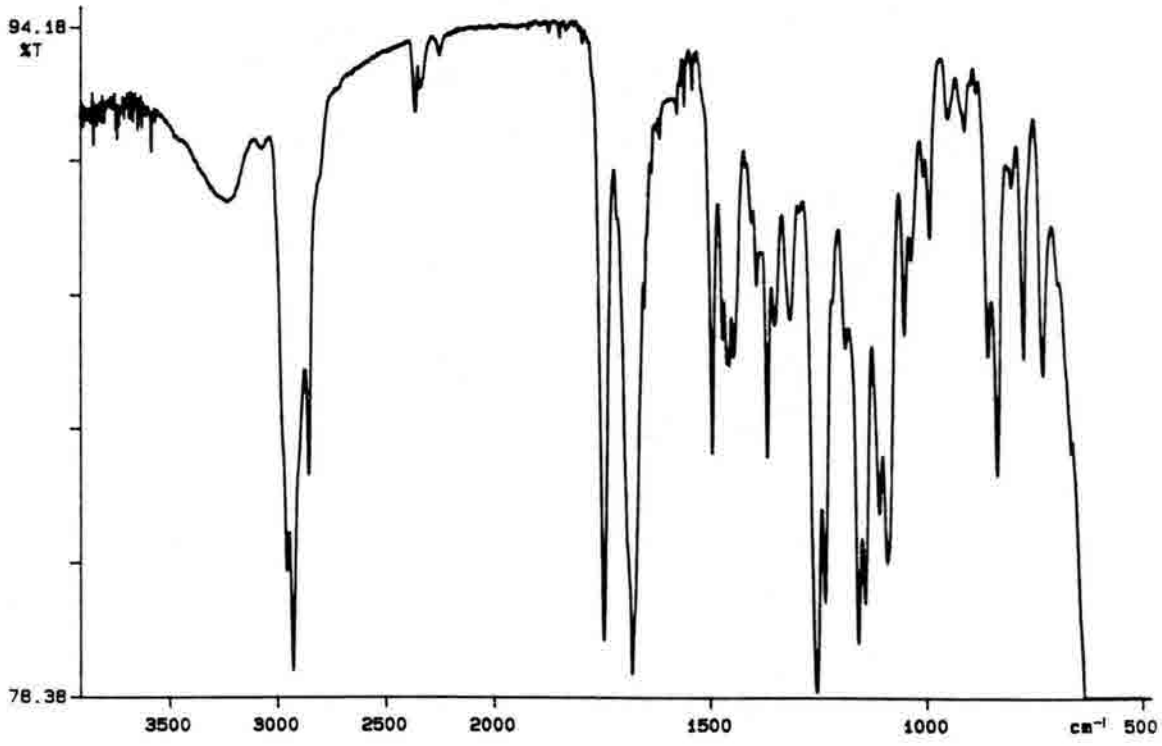
4.18 (2H, m); 6.03 (2H, s, D_2O exch.); 6.78 (1H, d, J = 8.3Hz); 6.79 (1H, d, J =8.3Hz); 6.89 (2H, d, J = 8.3Hz);

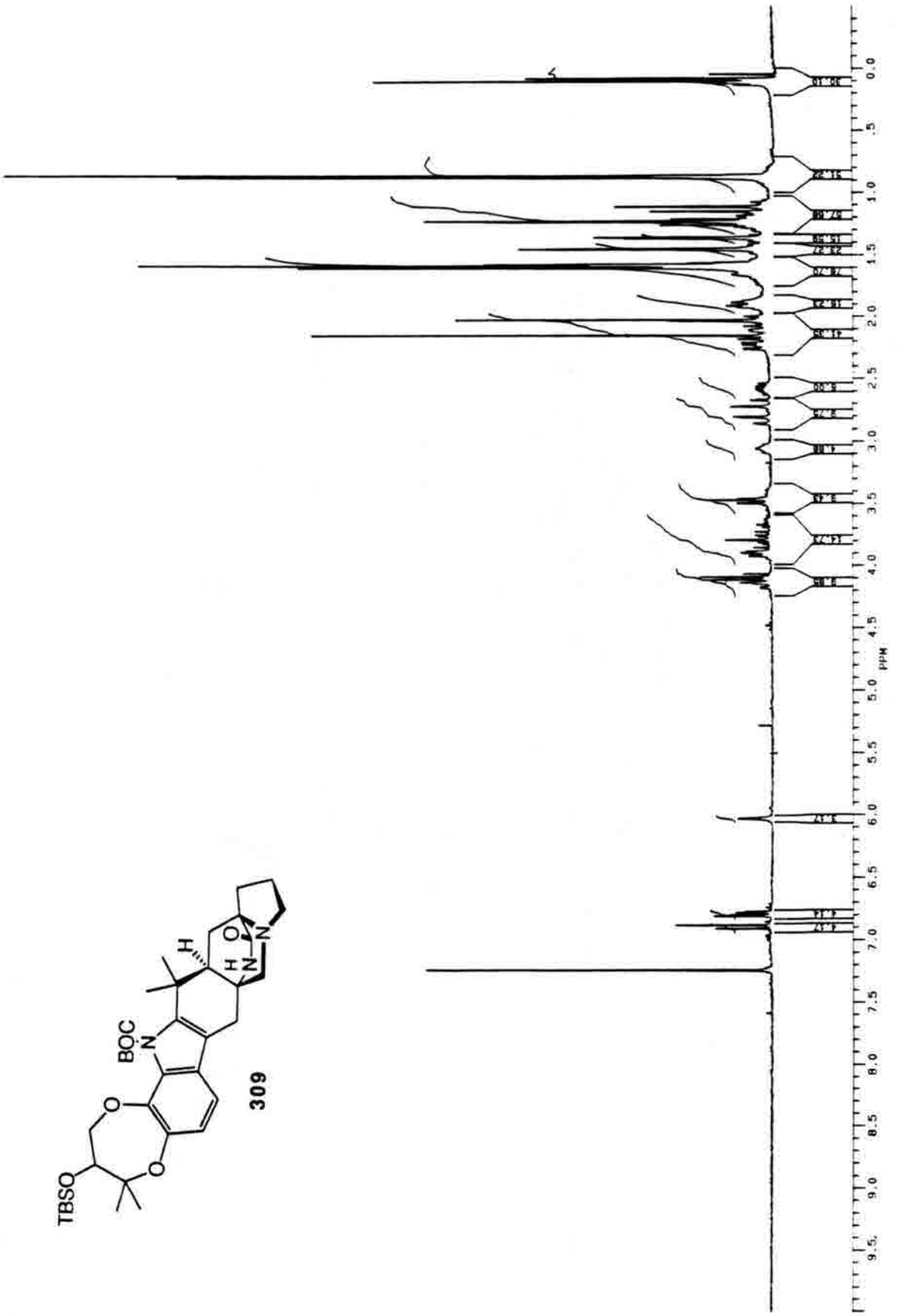
IR (neat) 3227, 2928, 1746, 1683, 1597, 1371, 1254, 1233, 1154, 1138, 1090, 836 cm^{-1}.

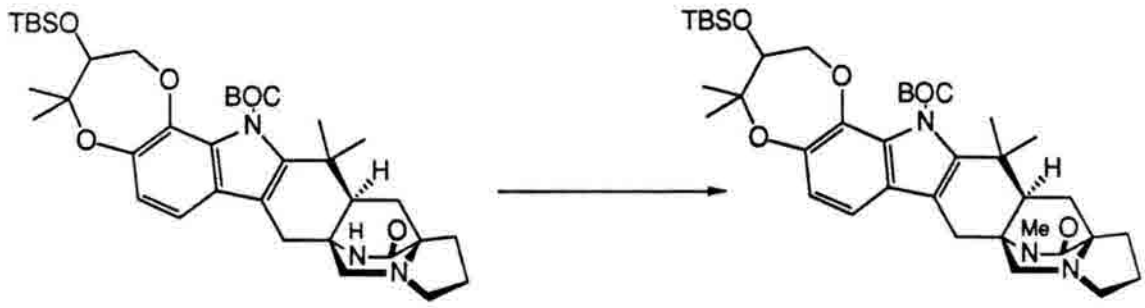
MS (EI) 665 *m/e* (rel intensity) 665 (M^+, 0.3) 565 (30.6) 521 (40.1) 164 (100).

microanalysis calc'd. for $C_{37}H_{55}N_3O_6Si$: C, 66.73; H, 8.32; N, 6.31; found: C, 66.50; H, 8.18; N, 6.33.

EI HRMS m/e 665.38365 ($C_{37}H_{55}N_3O_6Si$ requires 665.3860).




TBSO
BOC
309
PPM



309 **310**

1,1-Dimethylethyl-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octohydro-4,4,15,15,18-pentamethyl-17-oxo-11*H*,16*H*,8a,13a-(Iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-a]indolizino [6,7-h]carbazole-16-carboxylate (310)

To a stirred solution of **309** (147.5mg, 0.2217mmol, 1.0eq) in DMF (2.2mL) under Ar at 0 °C was added NaH (13.3mg, 0.554mmol, 2.5eq). After 5 minutes MeI (27.6uL, 0.443mmol, 2.0eq) was syringed in dropwise. The mixture was stirred for 4 hours, when a small amount of water and mercaptoethanol (21.6uL) were added. After a few minutes the mixture was diluted with water and extracted with 1:1 hexanes/ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. chromatography; radial, 1:2 hexanes/ethyl acetate. yield, 146.9mg, 98%. An analytical sample was obtained by PTLC, 1:1 ethyl acetate/hexanes, (white crystalline solid).

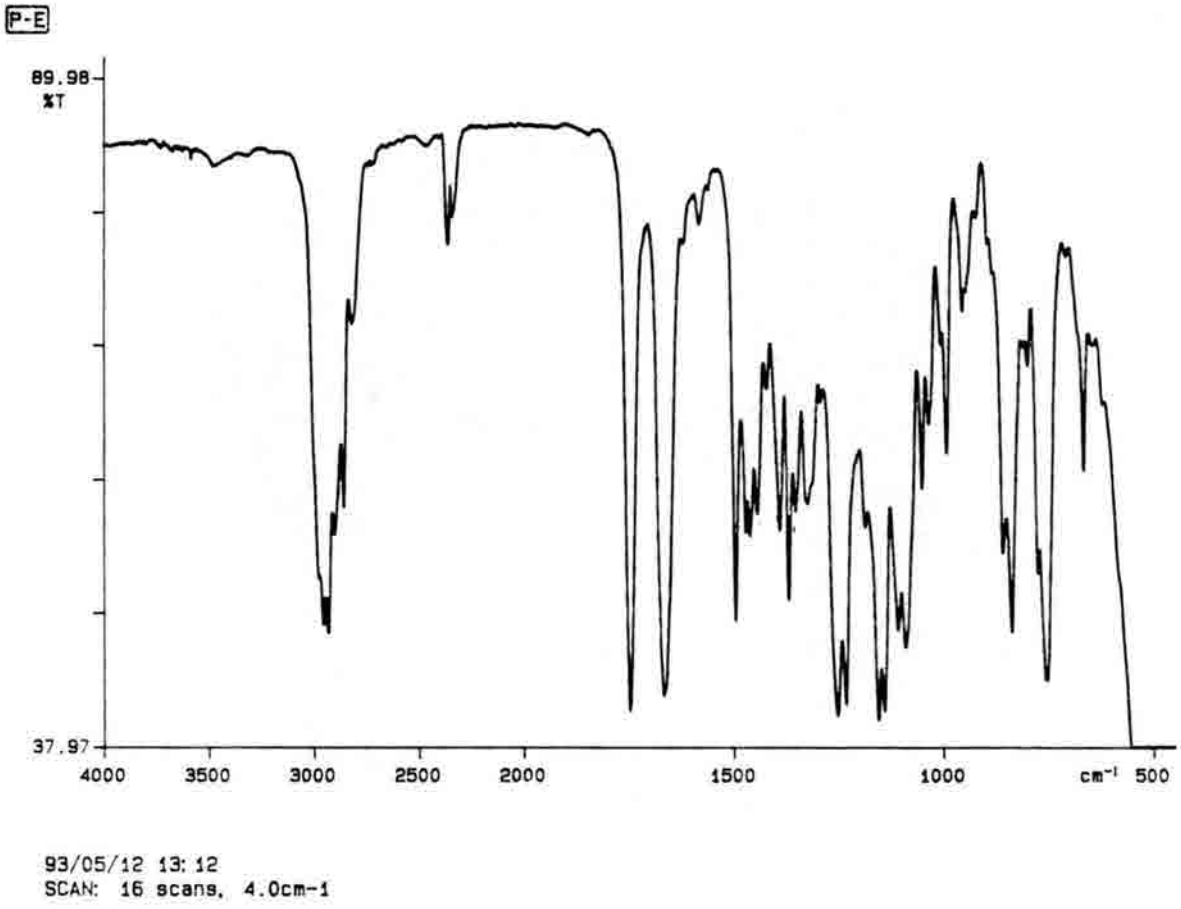
^{1}H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 0.089 (6H, s); 0.11 (6H, s); 0.87 (9H, s); o.88 (9H, s); 1.13 (3H, s); 1.15 (3H, s); 1.36 (3H, s); 1.37 (3H, s); 1.46 (6H, s); 1.59 (9H, s); 1.61 (9H, s); 1.86–2.06 (10H, m); 2.09–2.20 (6H, m); 2.61–2.70 (2H, m); 2.747 (1H, ½ ABq, J = 15.4Hz); 2.754 (1H, ½ ABq, J = 15.4Hz); 2.30–3.05 (2H, m); 3.05 (6H, s); 3.14 (2H, ½ ABq, J = 15.4Hz); 3.39 (2H, d, J = 10.5Hz); 3.74–3.85 (2H, m); 3.89–3.93 (2H, m); 4.07–4.18 (2H, m); 6.797 (1H, d, J = 8.3Hz); 6.804 (1H, d, J = 8.3Hz); 6.93 (2H, d, J = 8.3Hz).

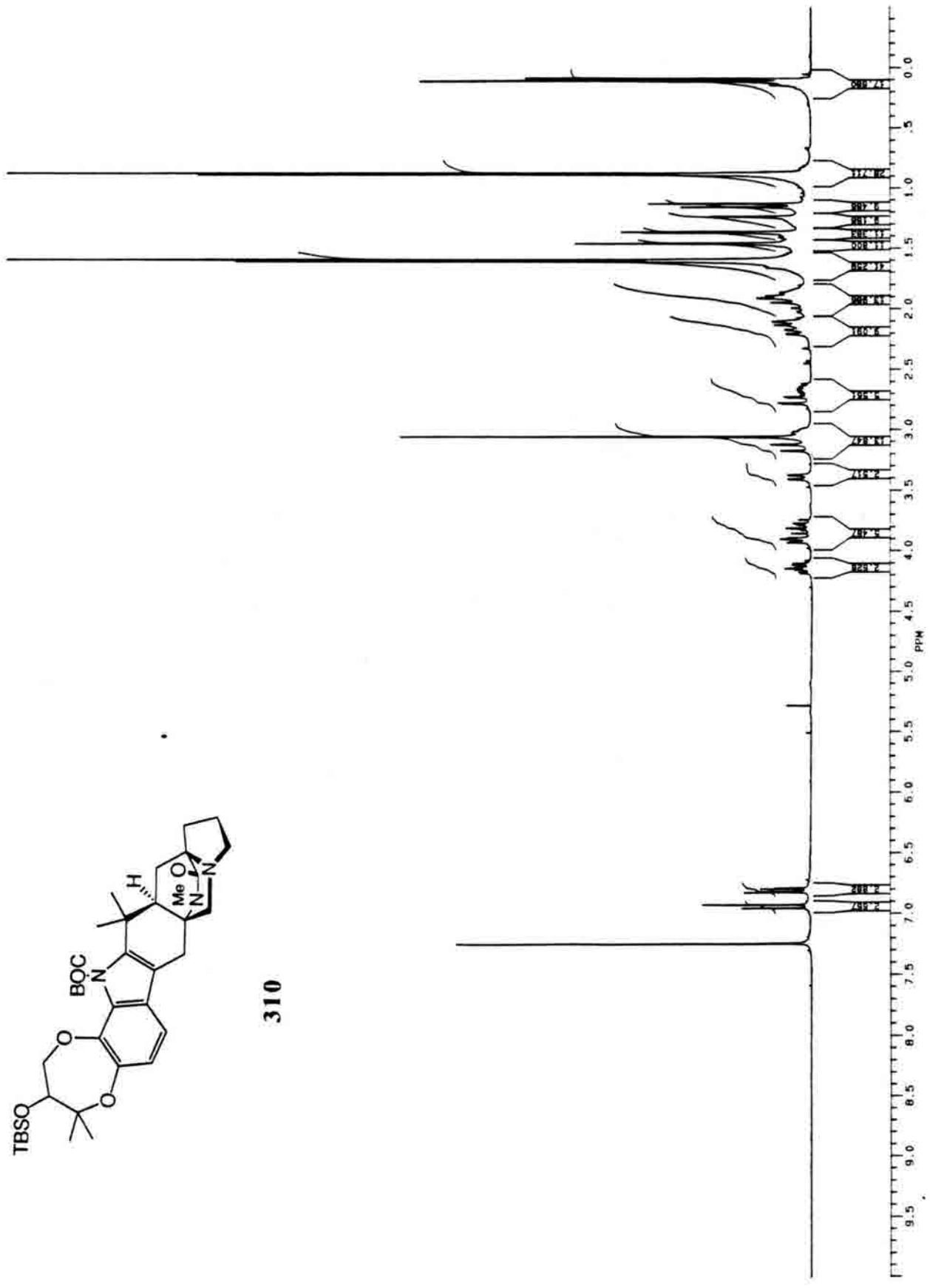
IR (neat) 2921, 1747, 1665, 1496, 1371, 1251, 1235, 1158, 1142, 1108, 1093, 837, 755 cm^{-1}.

MS (EI) 679 *m/e* (rel intensity) 679 (M^+, 2.1) 579 (4.2) 520 (4.2) 178 (100).

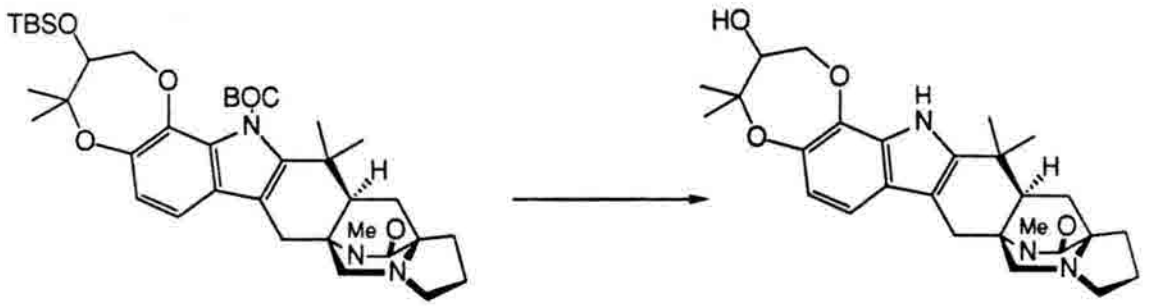
microanalysis calc'd. for $C_{38}H_{57}N_3O_6Si$: C, 67.12; H, 8.45; N, 6.18 found: C, 67.33; H, 8.27; N, 6.44.

EI HRMS m/e 679.4008 ($C_{38}H_{57}N_3O_6Si$ requires 679.4017).





310



310 **311**

3-[Hydroxy]-3,4,8,12,13,14,14a,15-octohydro-4,4,15,15,18-pentamethyl-17-oxo-11*H*,16*H*,8a,13a-(Iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-a]indolizino [6,7-h]carbazole (311)

To a stirred solution of **310** (294.7mg, 0.4338mmol, 1.0eq) in CH_2Cl_2 (8.7mL) at 0 °C under Ar was added TFA (2.77mL, 34.7mmol, 80.0eq) dropwise. The solution was stirred for 15 hours, maintaining the temperature at 15 °C. At this time the solution was stripped down, diluted with ethyl acetate, washed with $NaHCO_3$ (sat), brine and dried over Na_2SO_4. chromatography; radial, ethyl acetate. yield, 194.8mg, 96%. An analytical sample was obtained by PTLC, 1:1 ethyl acetate/hexanes, (white crystalline solid).

^1H NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 1.21 ((3H, s); 1.23 (3H, s); 1.29 (2H, s); 1.32 (3H, s); 1.42 (3H, s); 1.45 (3H, s); 1.54 (6H, s); 1.88–2.00 (10H, m); 2.07–2.22 (6H, m); 2.63–2.72 (2H, m); 2.79 (1H, ½ ABq, J = 15.1Hz); 2.80 (1H, ½ ABq, J = 15.1Hz); 3.01–3.07 (4H, m, 2H D_2O exch.); 3.07 (6H, s); 3.17 (1H, ½ ABq, J = 15.1Hz); 3.19 (1H, ½ ABq, J = 15.4Hz); 3.37–3.43 (2H, m); 3.62 (2H, br. s); 4.20 (2H, dd, J = 4.4, 12.3Hz); 4.29 (1H, dd, J = 4.0, 12.3Hz); 4.31 (1H, dd, J = 4.0, 12.3Hz); 6.750 (1H, d, J = 8.4Hz); 6.753 (1H, d, J = 8.3Hz); 7.01 (2H, d, J = 8.4Hz); 8.01 (2H, s, D_2O exch.).

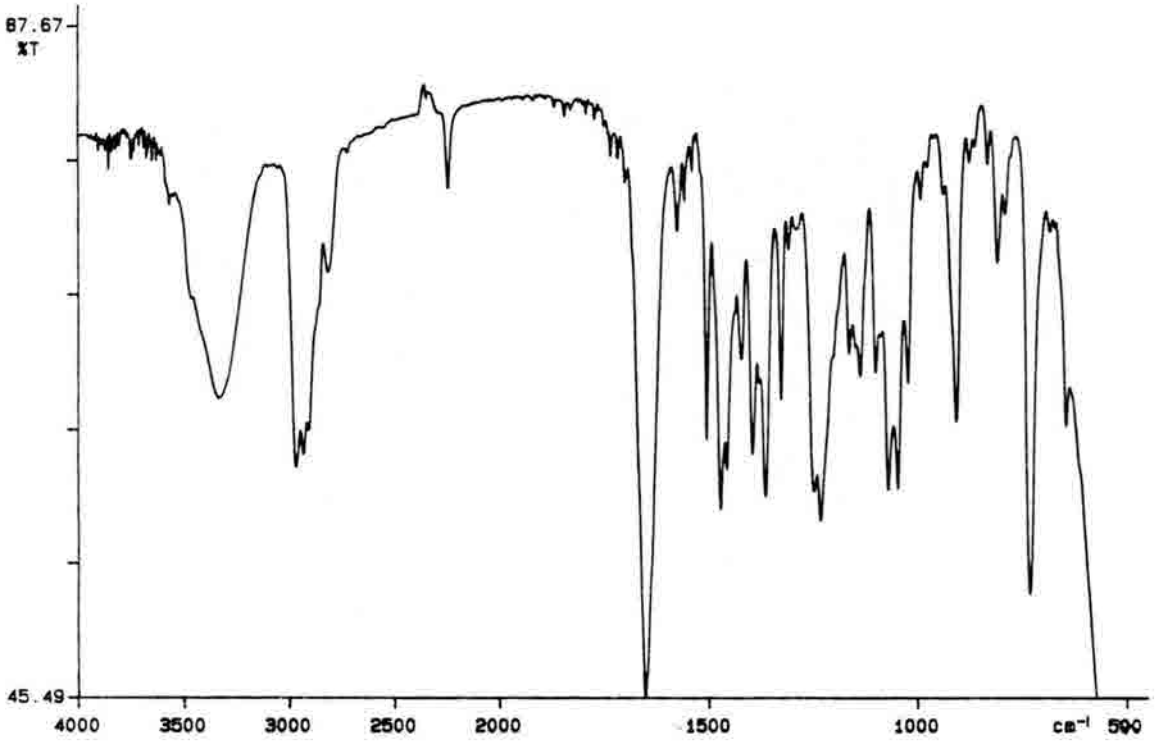
^{13}C NMR (300MHz) ($CDCl_3$) (mixture of two diastereomers) δ 14.0, 20.8, 22.6, 23.9, 24.4, 24.5, 24.7, 25.1, 27.7, 27.9, 30.2, 30.3, 31.3, 34.4, 45.9, 54.3, 57.4, 60.0, 60.2, 64.0, 71.0, 75.5, 76.6, 77.0, 77.4, 79.5, 104.6, 112.2, 116.17, 116.22, 125.0, 129.2, 137.2, 140.4, 141.6, 171.0, 174.3.

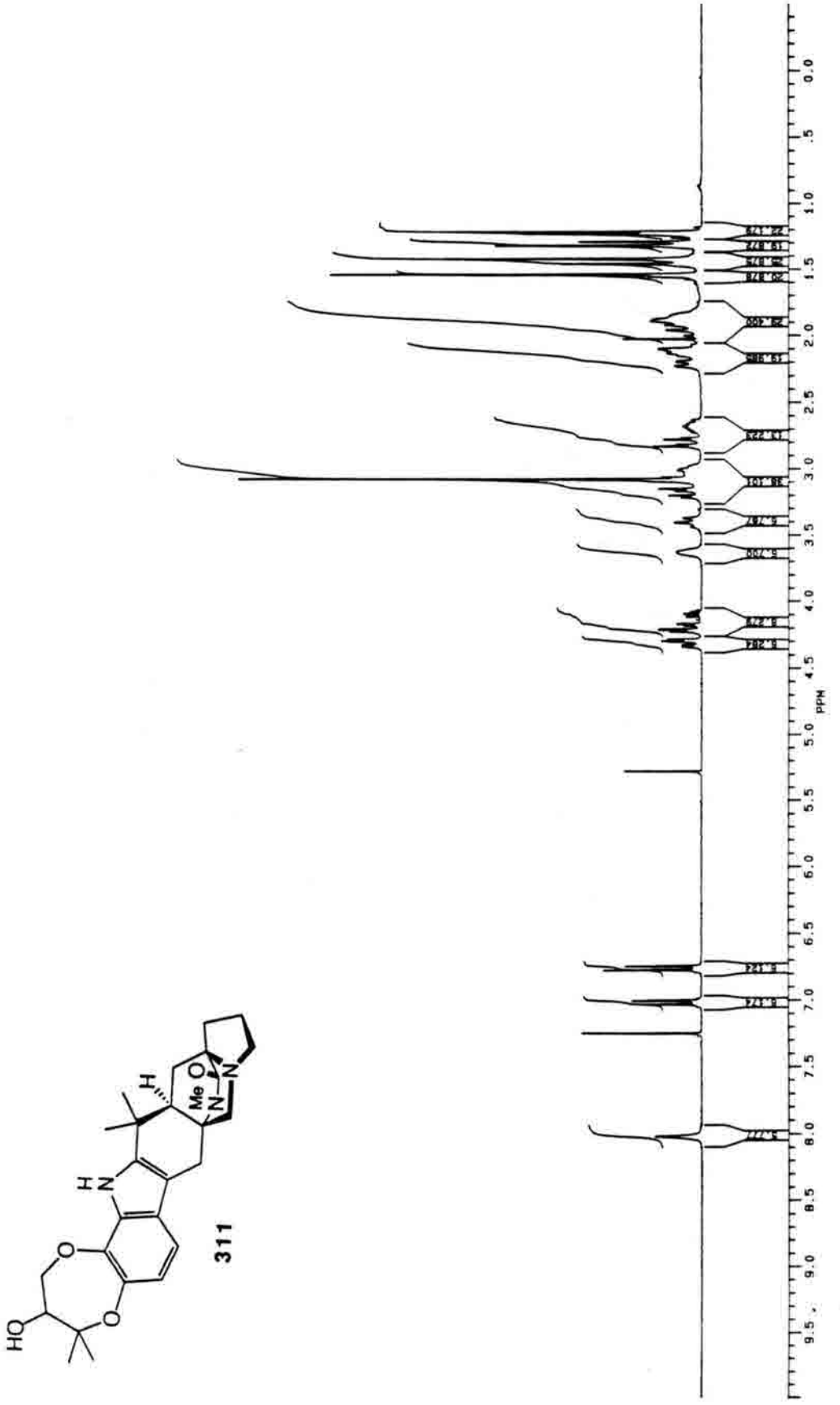
IR (neat) 3324, 2954, 1654, 1507, 1474, 1365, 1235, 1071, 1049, 908, 733 cm^{-1}.

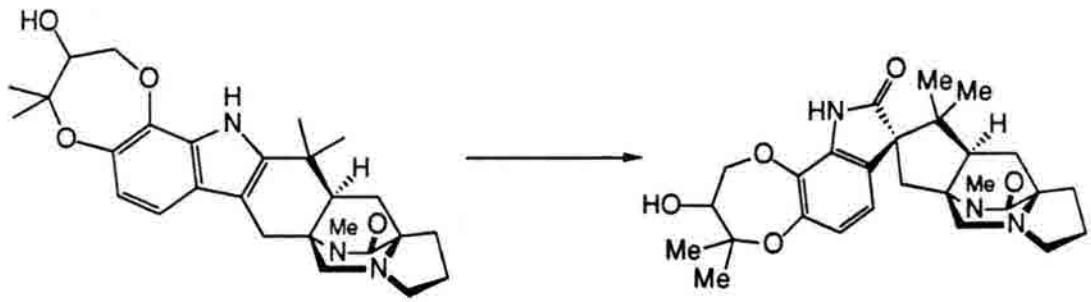
microanalysis calc'd. for $C_{27}H_{35}N_3O_4Si$: C, 69.65; H, 7.58; N, 9.02 found: C, 69.54; H, 7.66; N, 8.89.

MS (EI) 465 *m/e* (rel intensity) 465 (M^+, 9.7) 406 (14.5) 287 (11.8) 178 (100).

EI HRMS m/e 465.2625 ($C_{27}H_{35}N_3O_4Si$ requires 465.2628).




HO
O
O
H
N
H
Me
O
N
N
311
PPM



311 **319**

14-Deoxy-24,25-dihydro-25-hydroxy-17-Norparaherquamide (319)

To a stirred solution of **311** (23.8mg, 0.0511mmol, 1.0eq) in CH_2Cl_2 (1.0mL) was added Et_3N (6.7μL, 0.056mmol, 1.1eq) and t-butyl hypochlorite (7.8μL, 0.056mmol, 1.1eq) under Ar at 0 °C. After 0.5 hours the solvent was removed and the crude oil taken up in a solution of THF/H_2O/TFA (95:4:1). The resulting solution was refluxed for one hour, poured into a separatory funnel, diluted with ethyl acetate and washed with $NaHCO_3$ (sat) and brine. The organic layer was isolated and concentrated to dryness. chromatography; PTLC, 20:1 CH_2Cl_2/MeOH. yield; **319** (The product was a glassy solid), 10.5mg, 43%, **320**, 4.8mg, 19%.

This experiment was performed by professor J.-F. Sanz-Cervera.

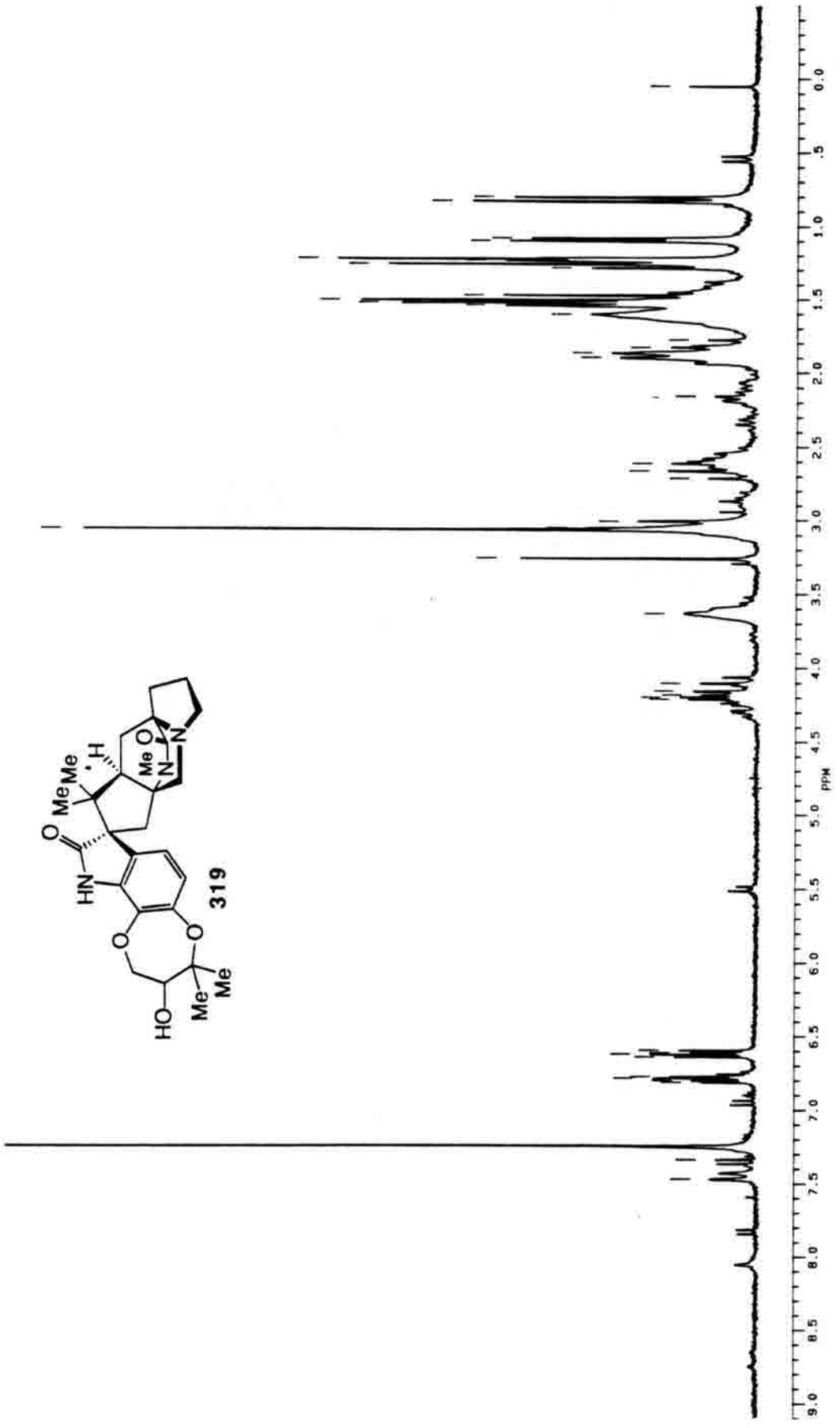
To a stirred solution of **311** (99mg, 0.21mmol, 1.0eq) in pyridine (4mL) at -15 °C under Ar was added t-BuOCl (37μL, 0.319mmol, 1.5eq). After 2 hours the solvent was removed (vacuum aspiration) to give the crude chloroindolenine.. yield; quant, 106mg.(as a mixture of epimers). The majority of the crude chloroindolenine (71mg, 0.14mmol, 1.0eq) was dissolved in THF (10mL) and water (1mL). This was followed by toluene sulfonylchloride monohydrate (135mg, 0.41mmol, 15eq). The resulting yellow solution was refluxed for 20 minutes and diluted with ethyl acetate and aq. K_2CO_3. The organic layer was isolated washed with brine, dried over Na_2SO_4 and concentrated to dryness. chromatography; PTLC, 20:1 CH_2Cl_2/MeOH, yield (from the chloroindolenine); **319**, 52mg, 76%, **320**, 2.7mg, 4%

^{1}H NMR (300MHz) ($CDCl_3$) mixture of two diastereomers δ TMS 0.80 (3H, s); 0.83 (3H, s); 1.08 (3H, s); 1.10 (3H, s); 1.22 (3H, s); 1.26 (3H, s); 1.50 (3H, s): 1.52 (3H, s); 1.40–1.60 (8H, m); 1.77–1.93 (8H, m); 2.05–2.21 (2H, m); 2.55–2.71 (4H, m); 3.02–3.10 (4H, m); 3.06 (6H, s); 3.63 (4H, br s, 2H D_2O exch.); 4.05–4.24 (4H, m); 6.60 (1H, d, J = 8.1Hz); 6.62 (1H, d, J = 8.2Hz); 6.78 (1H, d, J = 8.1Hz); 6.79 (1H, d, J = 8.2Hz); 7.42 (1H, s, D_2O exch.); 7.45 (1H, s, D_2O exch.).

IR (neat) 3333, 2974, 2933, 1703, 1651, 1646, 1631, 1456, 1395, 1323, 1200, 1046, 903 728 cm^{-1}.

MS (EI) 481 *m/e* (rel intensity) 481 (M^+, 0.7) 422 (20.7) 421 (15) 135 (48).133 (100).

CI HRMS m/e481 ($C_{27}H_{35}N_3O_5$ requires 481.2578), [M + H] 482.2645 ($C_{27}H_{36}N_3O_5$ requires 482.2655).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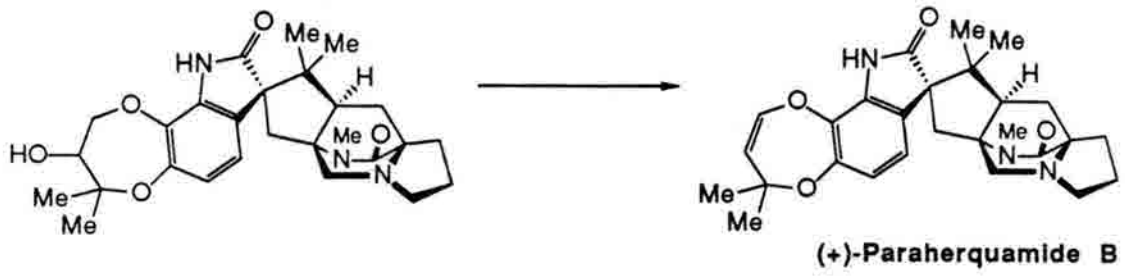
PPM



(+)-Paraherquamide B

319 **3**

(–)-Paraherquamide B (3)

To a stirred solution of **319** (10.8mg, 0.0224mmol, 1.0eq) in HMPA (0.2mL) under Ar at room temperature was added MTPI (20mg, 0.045mmol, 2.0eq). After four hours the reaction mixture was diluted with 1:1 hexanes/ethyl acetate and washed with water and brine . The organic layer was dried with Na_2SO_4 and concentrated. chromatography; PTLC, 20:1 CH_2Cl_2/MeOH. The product was a foamy solid. yield; 3.0mg, 29%.

This experiment was performed by professor J.-F. Sanz-Cervera.

To a stirred solution of **319** (22.5mg, 00.0468mmol, 1.0eq) in DMPU (500μL) under Ar at room temperature was added MTPI (90mg, 0.20mmol, 4.0eq). After 16 hours KOH (10mL, 1M) was added and stirred an additional 10 minutes. The pH was adjusted to 2 (addition of HCl) and the mixture extracted with ethyl acetate. The reaction mixture was diluted with 1:1 hexanes/ethyl acetate and washed with water and brine . The organic layer was dried with Na_2SO_4 and concentrated. chromatography; PTLC, 20:1 CH_2Cl_2/MeOH, yield of **3**; 17.1mg, 79%.

^{1}H NMR (300MHz) ($CDCl_3$) δ TMS 0.82 (3H, s); 1.09 (3H, s); 1.40 (3H, s); 1.41 (3H, s); 1.64 (1H, dd, J = 9.7, 12.4Hz); 1.73–1.92 (4H, m); 1.82 (1H, ½ ABq, J = 15.5Hz); 2.16 (1H, dd, J = 8.6, 17.8Hz); 2.54–2.59 (1H, m); 2.61 (1H, ½ ABq, J = 11.1Hz); 2.66 (1H, ½ ABq, J = 15.5Hz); 3.03–3.10 (2H, m); 3.05 (3H, s); 3.60 (1H, ½ ABq, J =

11.1Hz); 4.87 (1H, d, J = 7.7Hz); 6.30 (1H, d, J = 7.7Hz); 6.64 (1H, d, J = 8.2Hz); 6.78 (1H, d, J = 8.2Hz); 8.5 (1H, br s, D_2O exch.).

^{13}C NMR (300MHz) ($CDCl_3$) δ 20.7 (q); 23.8 (q); 26.2 (q); 28.2 (q); 28.8 (t); 29.8 (t); 29.9 (q); 37.2 (t); 46.1 (s); 52.8 (d); 53.8 (t); 59.5 (t); 63.0 (s); 65.2 (s); 67.4 (s); 79.7 (s); 115.0 (d); 117.2 (d); 120.3 (d); 125.3 (s); 132.5 (s); 135.3 (s); 139.0 (d); 146.0 (s); 172.9 (s); 183.1 (s).

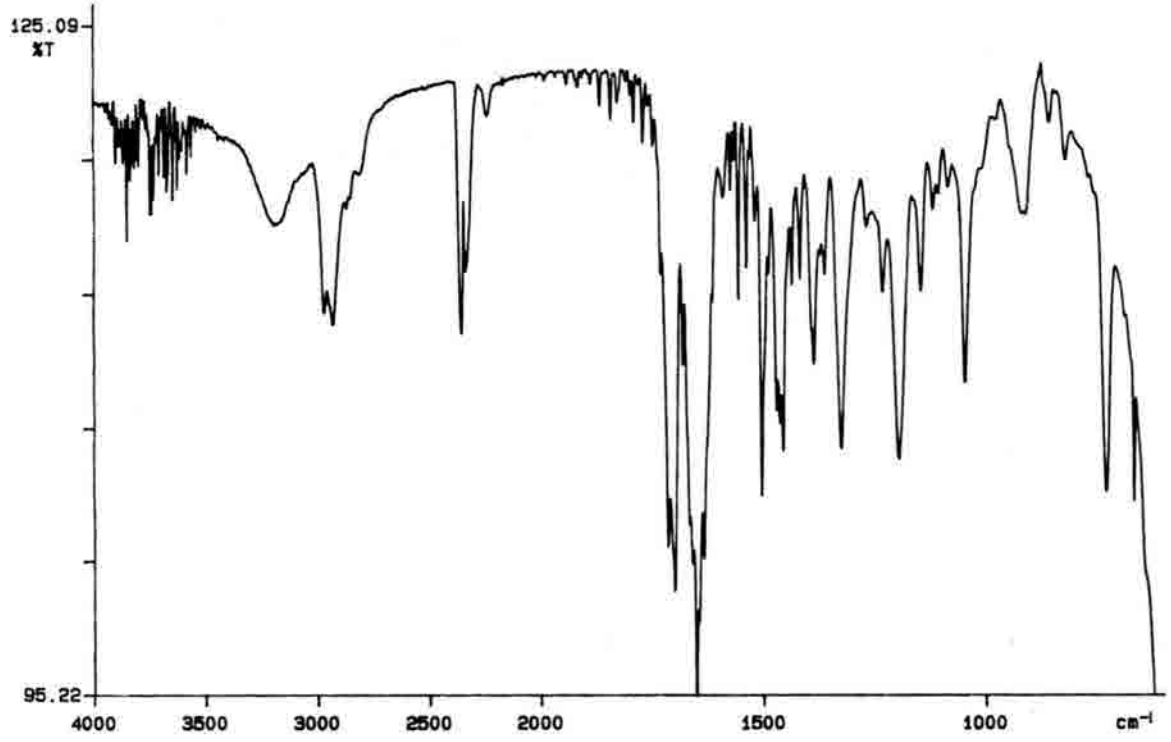
IR (neat) 3190, 2974, 2933, 1703, 1697, 1651, 1631, 1503, 1456, 1328, 1195, 1046 728 cm^{-1}.

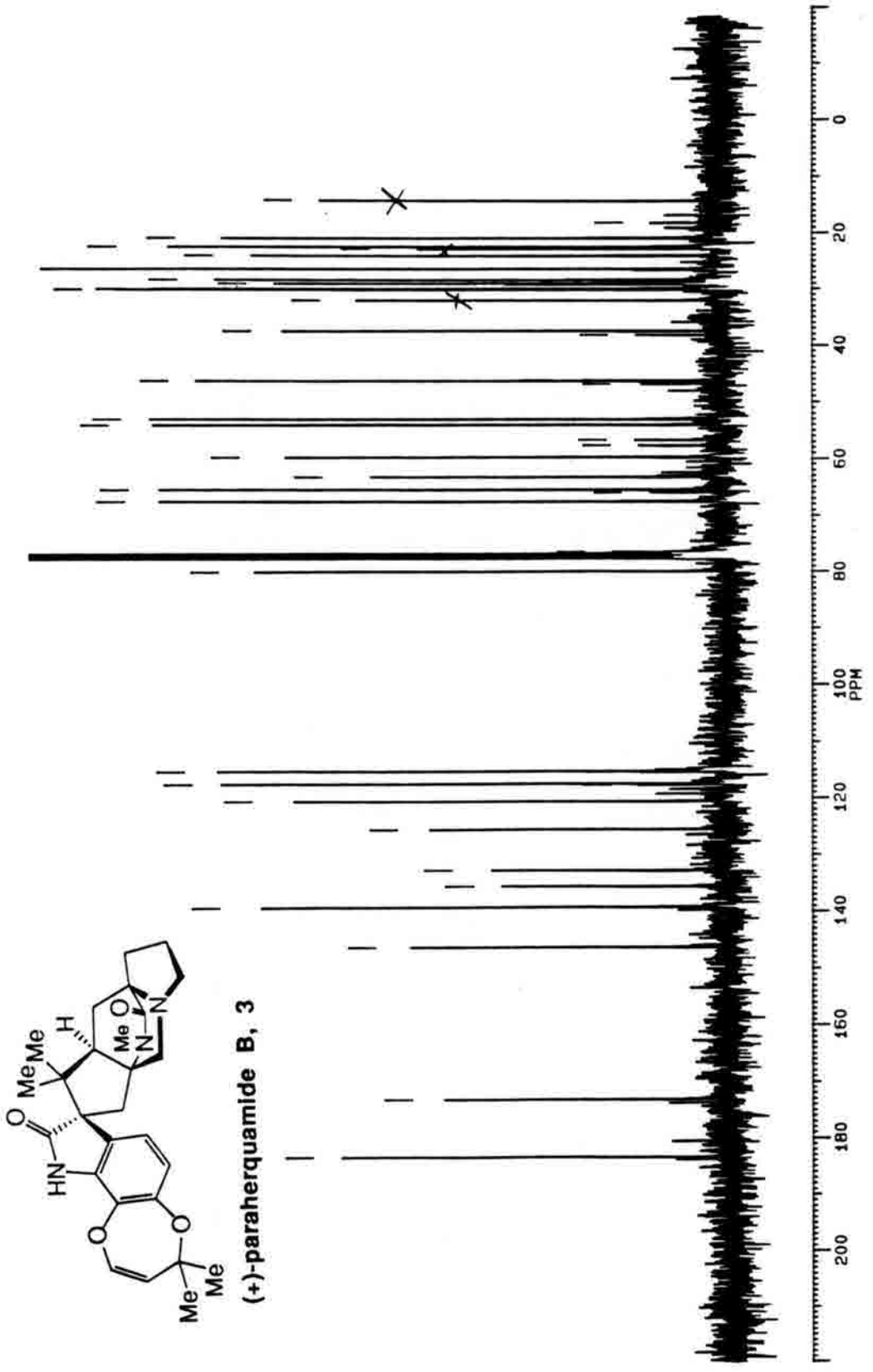
u.v. λ_{max} 226nm (ε = 30200).

$[\alpha]_{25}^{D}$ = + 0.4/7.75x10-3 = + 51.6 ($CHCl_3$, c = 0.008)

MS (EI) 463 *m/e* (rel intensity) 463 (M^+, 0.5) 404 (15.6) 135 (41.5) 133 (100).

EI HRMS m/e 463.2456 ($C_{27}H_{33}N_3O_4$ requires 463.2471).

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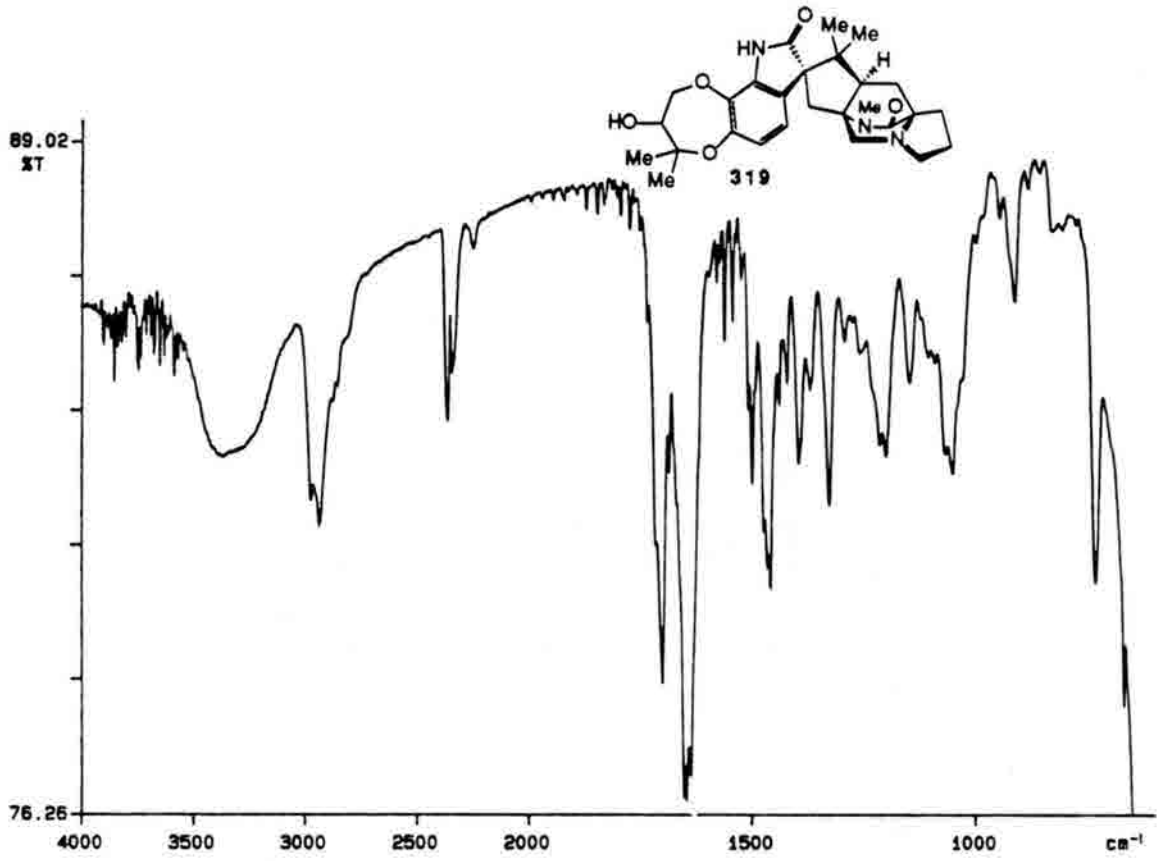
80
100
120
140
160
180
200
PPM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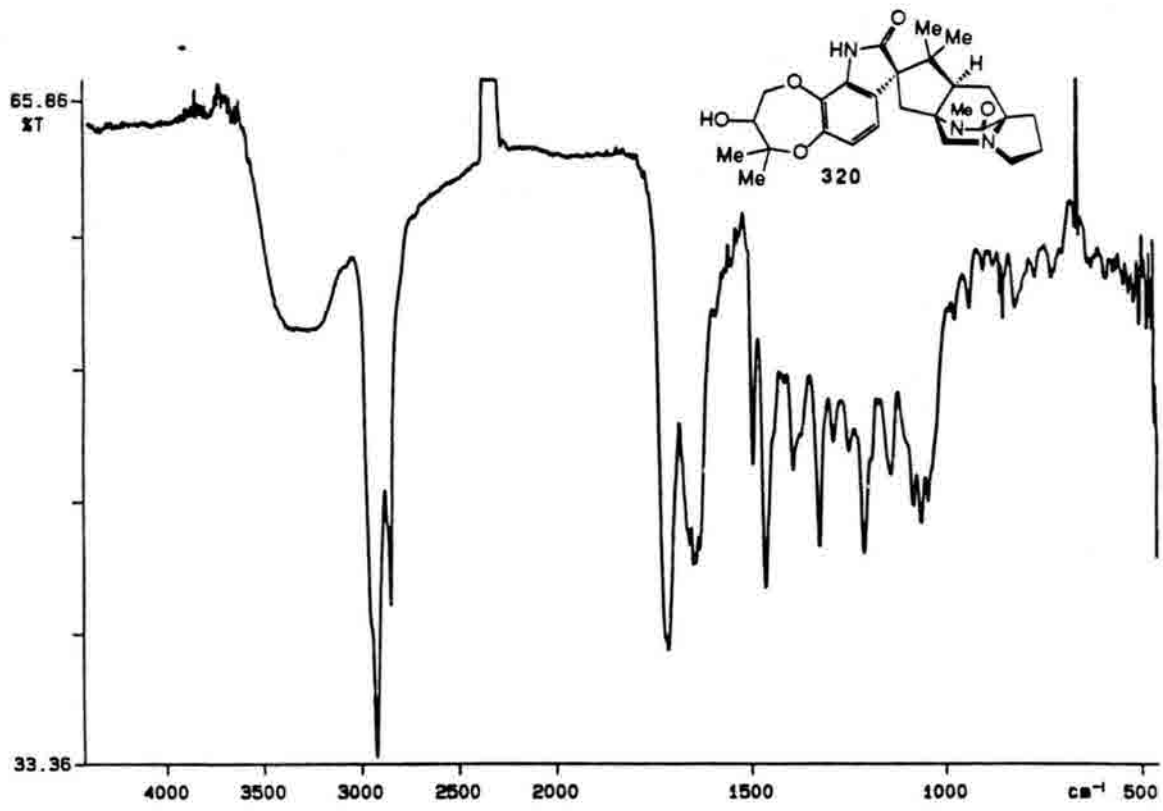
N
N
O
319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N
O
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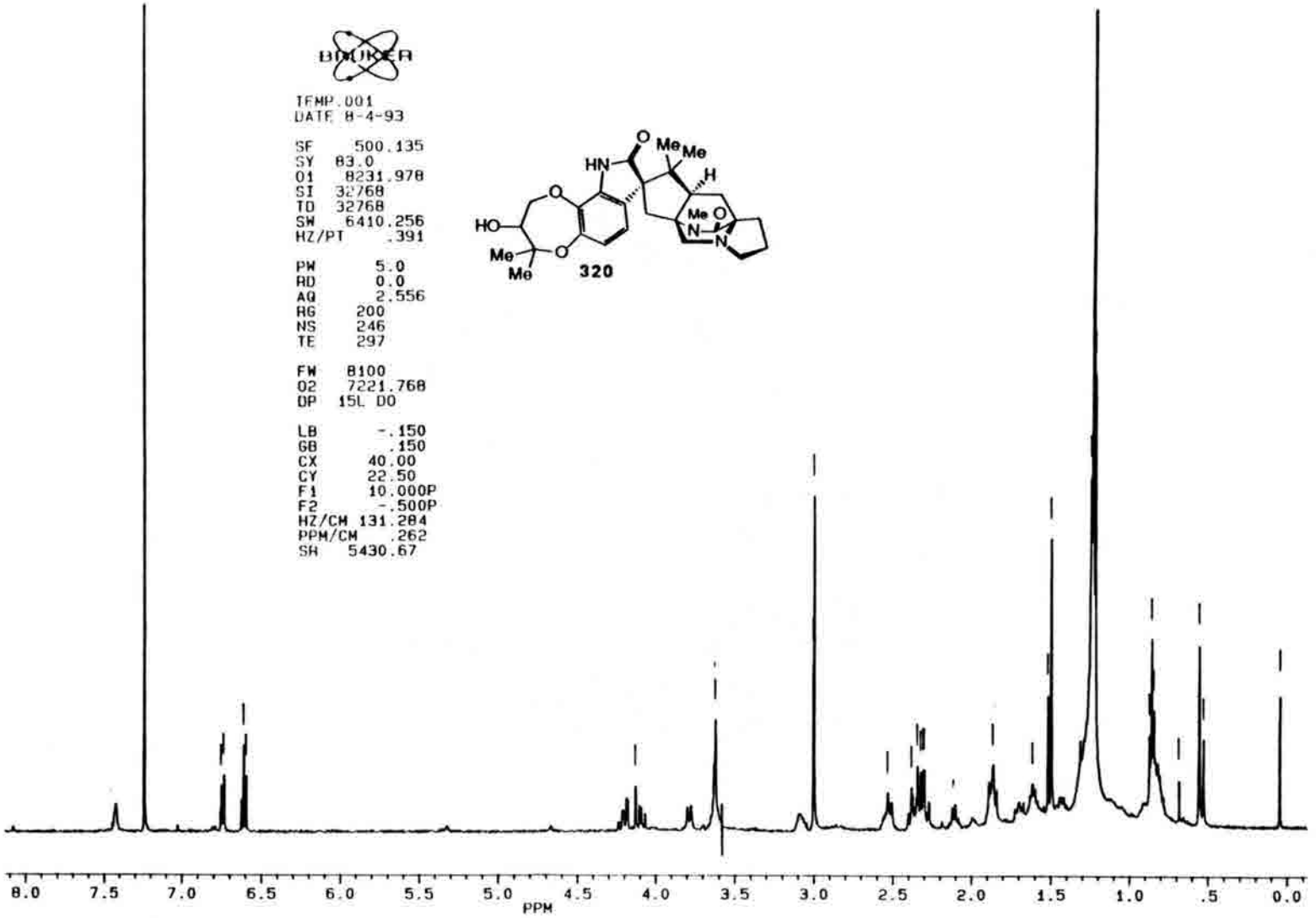
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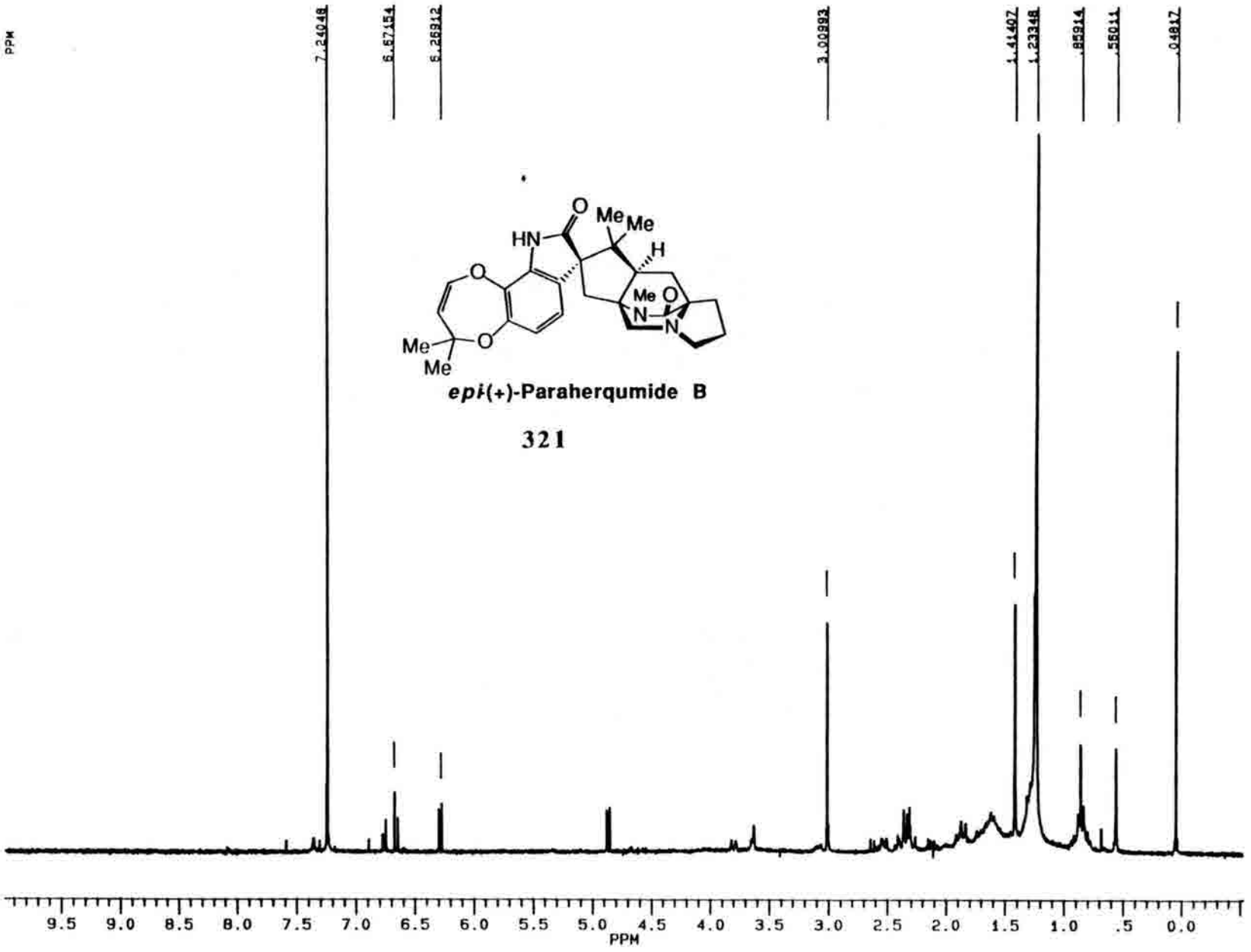
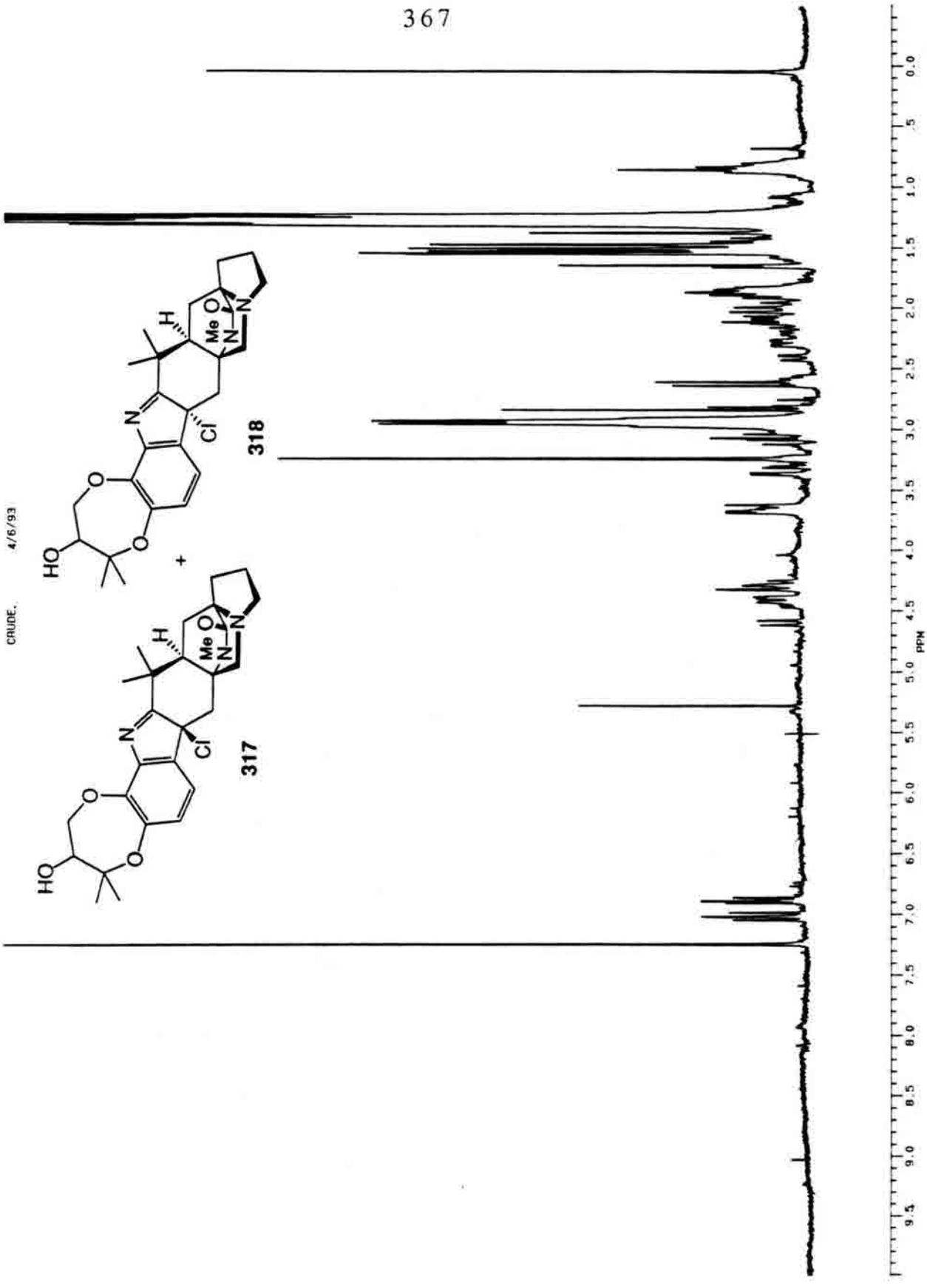


***epi*(+)-Paraherqumide B**

321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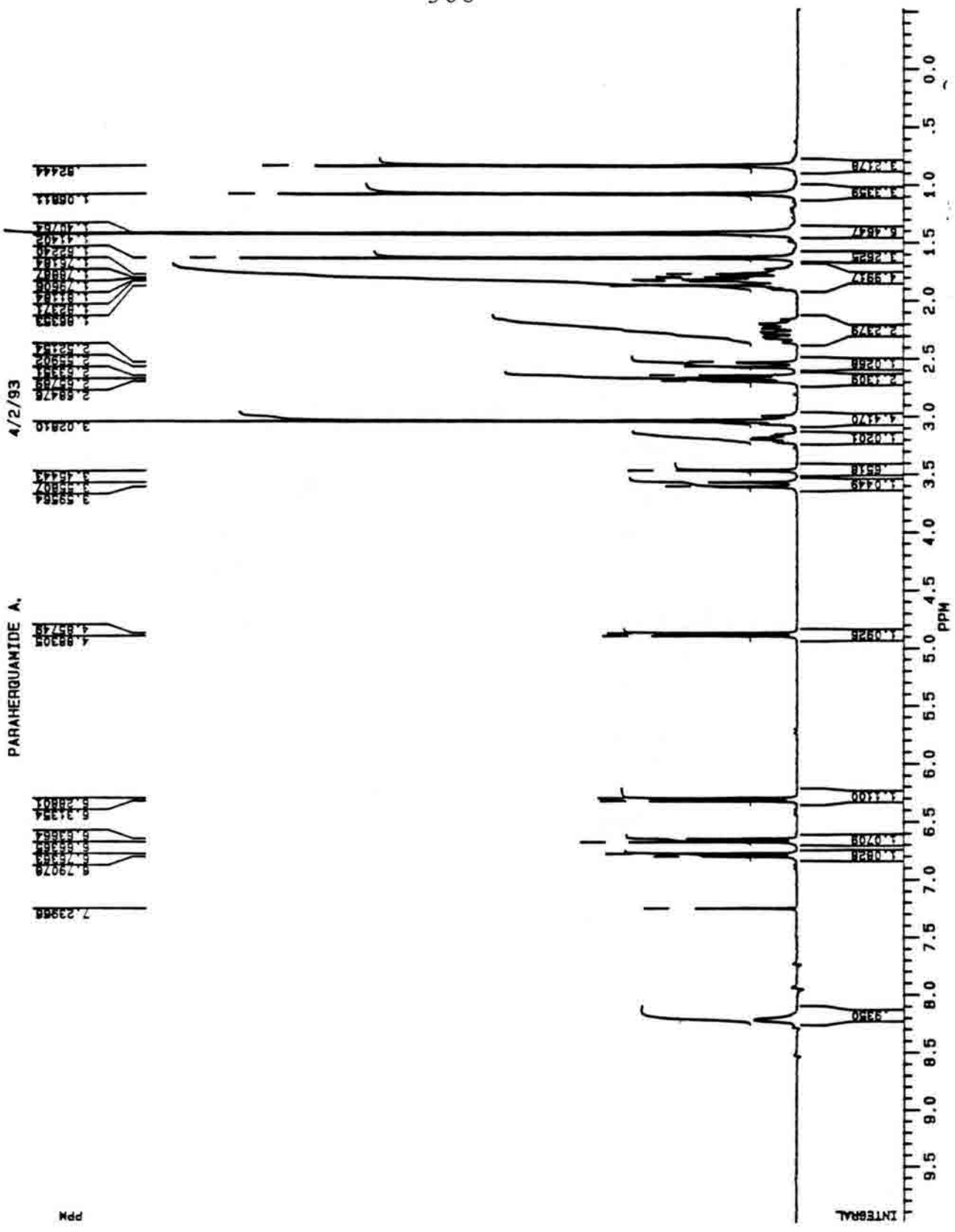
H
Cl
318
+
317
PPM


PARAHERQUAMIDE A.
4/2/93
PPM
INTEGRAL